Contents

Director-General's Message

It is my pleasure to present the progress of research activities of Indian Council of Medical Research (ICMR) for 2008 -2009. During the short stint at the ICMR, I have made efforts to reorganize the Council's various ongoing intramural and extramural activities. Steps have been taken to initiate newer activities for furthering the aims and objectives of the Council keeping in view the national health priorities and goals. The Department of Health Research, still in nascent stage, will be giving meaningful advise and directions to the Council for achieving the objectives of taking health research to the doorstep of the common man, among others, through translational research.

During the year, the ICMR School of Public Health was established at Chennai where Master of Public Health (MPH) was started. The Model Health Research Unit of National JALMA Institute of Leprosy and Other Mycobacterial Diseases, Agra established at Ghatampur, Kanpur is providing services to the rural areas of Kanpur and is serving as a model of transfer of technology to end users in a rural set up. The National Institute of Virology, Pune has set up two new Field Units at Gorakhpur and Alappuzha for investigating outbreaks of viral diseases.

Phase I HIV vaccine trial of TBC-M4 using modified vaccinia Ankara as the vector was completed in February 2008 by TRC, Chennai. The vaccine candidate was found to be safe and effective . Attempts are being made to develop suitable vaccines for other diseases also such as tuberculosis, malaria, *etc.*

A number of new activities were taken up for achieving the target of health for all and for serving rural, tribal and other marginalized populations. The Vector Control Research Centre, Puducherry has prepared a lymphatic filariasis transmission risk map for India. Various institutes and centres of the Council also undertook investigation of epidemic outbreaks occurring in the country.

The National Cancer Registry Project of the Council continues to collect data on cancers in the country. The significant finding during the year was decline in cancer cervix across all registries including rural registry at Barshi.

Nine Biomedical Informatics Centres of ICMR were set up at various institutes in the country during the period in record for research and training in bioinformatics.

A total of 1147 research projects and 548 research fellowships were funded by the Council during 2008 – 2009. The scientists of ICMR published 576 research papers in national and international journals during the calendar year 2008. The impact factor of the *Indian Journal of Medical Research* increased to 1.88 during the year, another significant achievement. A total of 5 patents were filed during 2008 -2009.

Dr V M Katoch
Director - General

Overview

During the year under review, the Council continued to surge ahead in the field of medical and health research. A number of new activities were taken up for achieving the target of health for all and for serving rural and tribal communities. Emphasis was placed on developing suitable vaccines for various diseases. The Council established the ICMR School of Public Health at Chennai where Master of Public Health (MPH) was started from July 2008.

Phase I HIV vaccine trial of TBC-M4 using modified vaccinia Ankara as the vector was completed in February 2008 by Tuberculosis Research Centre (TRC), Chennai. It was found that this vaccine candidate was safe in the two dosages that were tried and the higher dose induced 100% cell-mediated immune response in recipients.

As part of the goal of bringing modern health technology to the people a Model Rural Health Research Unit (MRHRU) of the National JALMA Institute of Leprosy and Other Mycobacterial Diseases (NJILOMD) at Agra has been established at Ghatampur, Kanpur in which medical treatment for tuberculosis, leprosy and filariasis is provided free of cost to all patients. The Unit will serve as a model for transfer of technology to end users in rural set up.

The National Institute of Cholera and Enteric Diseases (NICED), Kolkata continued to maintain its service components dedicated to antisera supply, bioinformatic analysis of molecular epidemiological and proteomic data, evaluation of clinical parameters of patients and vaccinated subjects, phage typing of *Vibrio cholerae* strains received for characterization from different regions of the country and abroad and investigation of epidemic outbreaks.

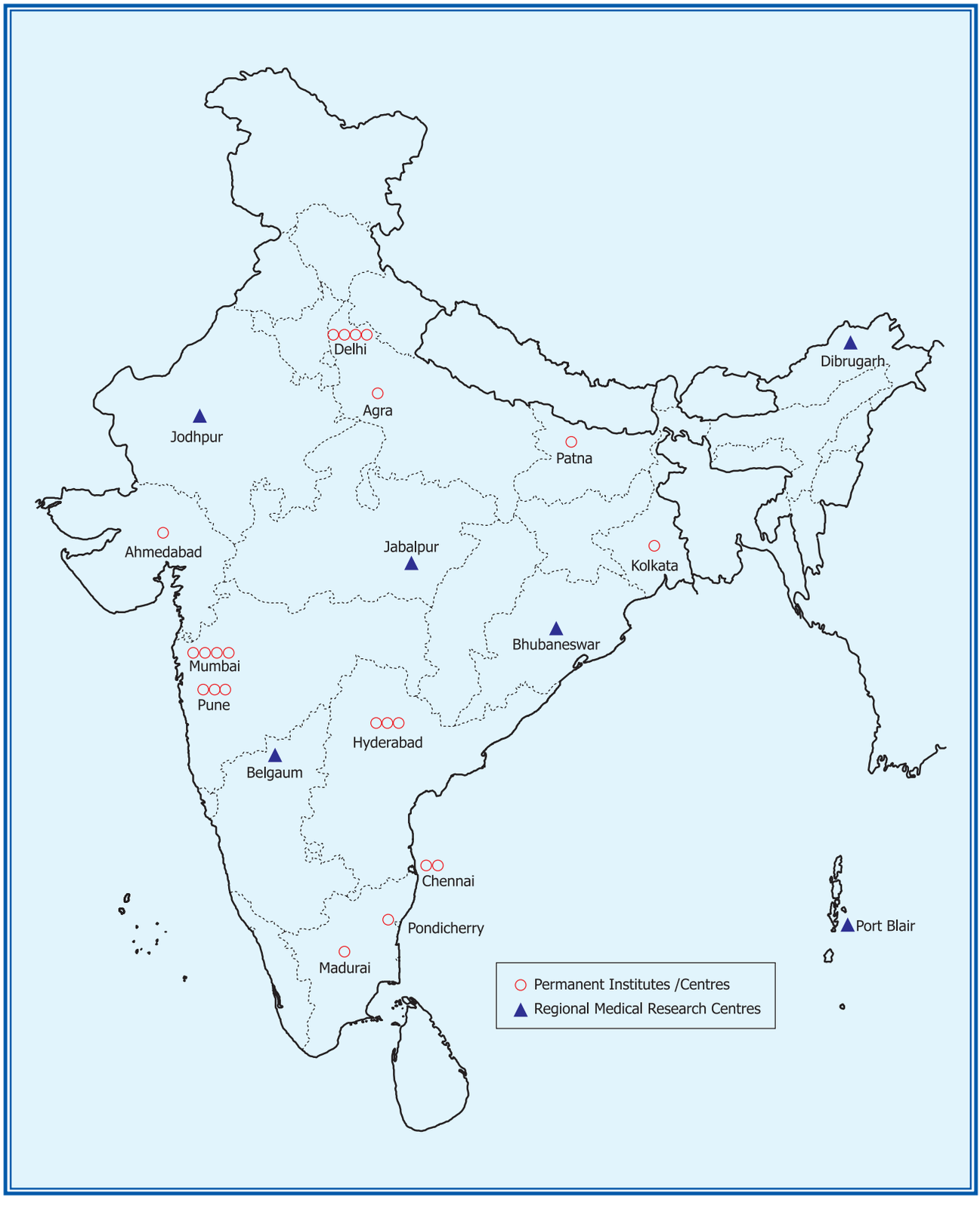
In studies done at National Malaria Research Institute (NIMR), New Delhi, it was found that 46% of the total infections are mixed due to both *P. falciparum* and *P. vivax*. Such an alarmingly high rate of mixe d malaria parasitic infection has been reported for the first time in India. Studies done at NIMR also revealed that the safety and efficacy of arterolane maleate and piperaquine phosphate combination is comparable to Coartem®, the current gold standard fixed dose combination for treatment of *falciparum* malaria.

A lymphatic filariasis transmission risk map has been generated for India, using the geo-environmental risk model (GERM) by Council's Vector Control Research Centre (VCRC) located at Puducherry.

National Institute of Virology (NIV), Pune established two new units at Gorakhpur, UP and Alappuzha, Kerala. Both units are functional and have actively participated in the investigation of acute encephalitis syndrome (AES) and Chikungunya outbreaks in Gorakhpur and Kerala respectively.

Under the project on home based management of young infants, trained village level workers called *Shishu Rakshaks* (SR) and *Anganwadi* workers (AWW) delivered intervention in rural areas of five states in the country by conducting survey of eligible women and registering pregnant women at 5th month through house to house survey.

An ICMR Validation laboratory has been set up to act as a referral laboratory for training and external quality maintenance in research work, to take up standardization of appropriate methodologies and to facilitate / carry out need based nutrition research.



ICMR Institutional Network

The bio-effect of ultra-rice on iron status of beneficiaries of mid-day meal programme was evaluated. Rice fortified with iron when given in the mid-day meal to school children for over a year resulted in significant improvement in their haemoglobin levels and iron stores.

The data collected by National Cancer Registry Project of the Council revealed that among males, cancers of the prostate, colon, rectum and liver showed significant increase in incidence rates while among women, cancers of the breast, corpus uteri, ovary, thyroid, gall bladder and lung have shown a rise. Cancer cervix recorded a decline in incidence rates across all registries including rural registry at Barshi.

The Indian Journal of Medical Research published by ICMR is available full-text free on the internet. Its impact factor increased to 1.88 compared to last year's 1.67. The Council is bringing out a series of Reviews on Indian Medicinal Plants.

Nine Biomedical Informatics Centres (BIC) of ICMR located at various Institutes in the country are working on database development, research in bioinformatics and organizing training programmes in bioinformatics for scientists and medical professionals.

A total of five patents were filed with Indian Patent Office during 2008-2009 from intramural research done at ICMR institutes.

The Council initiated translational research activities and has requested its Institutes / Centres to provide a list of leads / processes / diagnostic kits resulting from research in their respective fields. These leads have been discussed and examined by the Council and are being processed for translation into National Health Care Programmes / clinical practice. Demonstration workshops on some of these research leads have also been organized for dissemination of the knowledge.

Under the project "Managing the Indo-German (ICMR-HGF) Science Centre for Infectious Diseases (IGSCID)" four collaborative projects were approved and funded.

A total of 1147 research projects and 548 research fellowships were funded by the Council during 2008-2009. ICMR scientists published 576 research papers in various national/ international journals during 2008.

Reproductive Health

The Council continued studies for development of new and improved technologies for male and female contraception, infertility and reproductive disorders, reproductive tract infections, maternal, adolescent and child health. Major studies in the field are being carried out by Council's National Institute for Research in Reproductive Health (NIRRH) at Mumbai.

FERTILITY REGULATION

Basic Research

Identification and Characterization of Sperm Antigens

Epididymal maturation is of strategic importance in the design of post testicular methods of male contraception as well as elucidation of the causes of male infertility. Study was undertaken at NIRRH, Mumbai to identify and catalogue domain specific epididymal sperm proteins using differential proteomics approach. Testicular sperm proteome (TSPome) and caudal sperm proteome (CSPome) were identified and compared. Fig.1 depicts the differential proteomic strategy adopted to identify the domain specific proteins. The data provides a useful repository which could be exploited to develop targets for post testicular immunocontraception or biomarkers for infertility diagnosis.

80kDa Human Sperm Antigen (80kDa HSA) and its Synthetic Peptides for Immunocontraception

Studies done at NIRRH on 80kDa HSA suggest that its expression is androgen regulated and peptide-1 of this antigen is immunogenic. Active immunization with this synthetic peptide resulted in reversible infertility in marmosets. Its antifertility effect is being studied in bonnet monkeys. One male bonnet monkey elicited gradual increase in antibody titer following active immunization with this peptide and showed antifertility activity. The animal is being monitored for restoration of fertility.

Functional Significance of FSH Modulators from Follicular Fluid

Octapeptide (OP) is a partial N-terminal 8 amino acid residue sequence of a protein purified from human

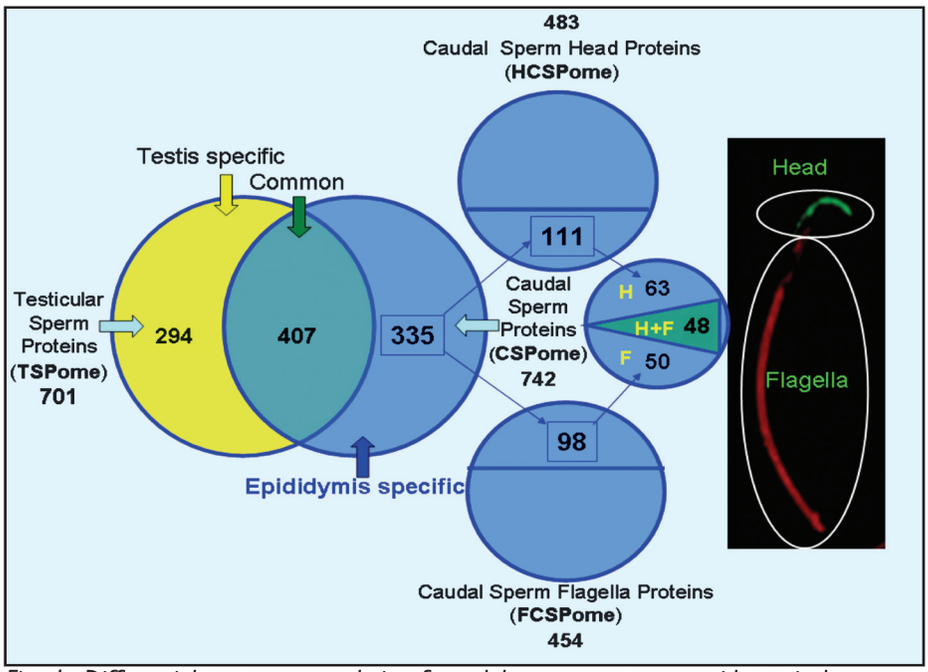


Fig. 1. Differential proteome analysis of caudal sperm proteome with testicular sperm proteome

ovarian follicular fluid. OP induces follicular atresia in mice and inhibits the binding of FSH to granulosa cells *in vitro*. Study was carried out at NIRRH to elucidate the structure of OP and to understand its mechanism of action in inhibiting FSH binding to its receptors. Structure designed by homology modeling predicted that the OP adopts a turn and random coil. To identify the probable binding sites, OP was docked with reported FSH-FSHR complex using ZDOCK algorithm. Studies revealed that the OP binds to the active site of FSHβL2-follicle stimulating hormone receptor hormone binding (FSHRHB) interaction – interface. (Fig. 2.)

Human Seminal Plasma Inhibin

Human seminal plasma inhibin (hSPI) is a 94 amino acid sperm coating antigen of molecular size 14kDa and is synthesized predominantly by prostate. Active/passive immunization with hSPI caused agglutination of rat epididymal spermatozoa and induced infertility. Antibodies to hSPI agglutinated rat, rabbit, monkey and human spermatozoa, *in-vitro*. Based on hydrophilicity and acrophilicity, synthetic peptides of hSPI were generated, synthesized, conjugated and polyclonal antibodies were generated in rabbits. N-terminal 1-17 amino acid (R-17) and C-terminal 28 amino acid (R-28) peptides were found to mimic the immunobiological properties of the native protein. Active immunization of rabbits with R-28 caused 60% reduction in fertility, while active immunization with R-17 peptide demonstrated 75% reduction in fertility in rats and caused reversible inhibition of sperm motility in bonnet monkeys. Immunization with R-17 did not alter hormonal profile, sperm production or any of the biochemical parameters. The studies suggest that hSPI and/or its synthetic peptides are potential candidates for development of a male contraceptive vaccine.

Clinical Research

Phase III Clinical Trial with Subdermal Contraceptive Single Rod Implant 'Implanon'

A total of 3142 women have been enrolled in the study so far and observed for 80, 897 woman months of use. Since the study was carried out in urban areas, majority of the acceptors are from urban (67.6%) and urban slum (15%) areas (only 17.4 % women were from rural areas). Of the total, 73% acceptors are interval cases and 27% accepted the method concurrently with elective termination of pregnancy. The interim results of the study indicate that implanon is quite efficacious as no method failure (pregnancy) has been reported till date. The cumulative continuation rates were found to be 90.3, 77.0, 70.5 and 64.0 per 100 users at 12 and 24, 30 and 36 months of use. Around one third (1194) women have completed 36 months of use. The predominant reason for discontinuation of the method was found to be menstrual disruptions.

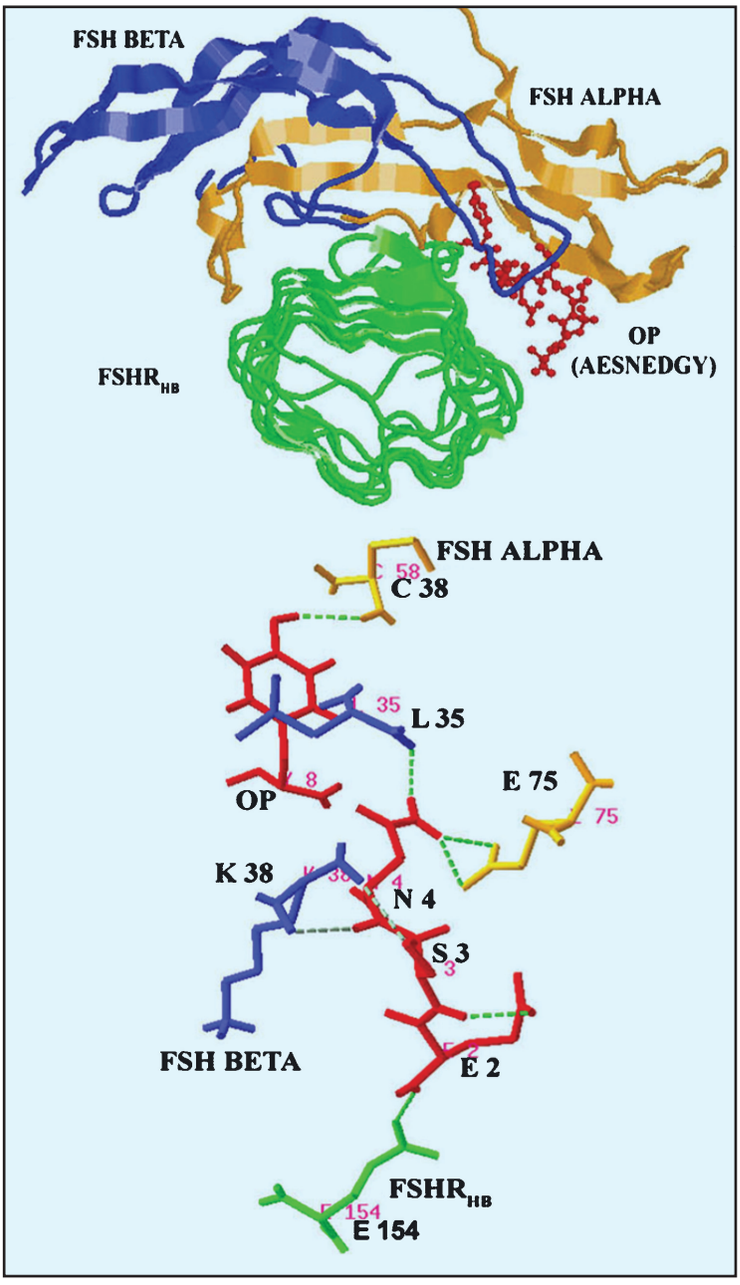
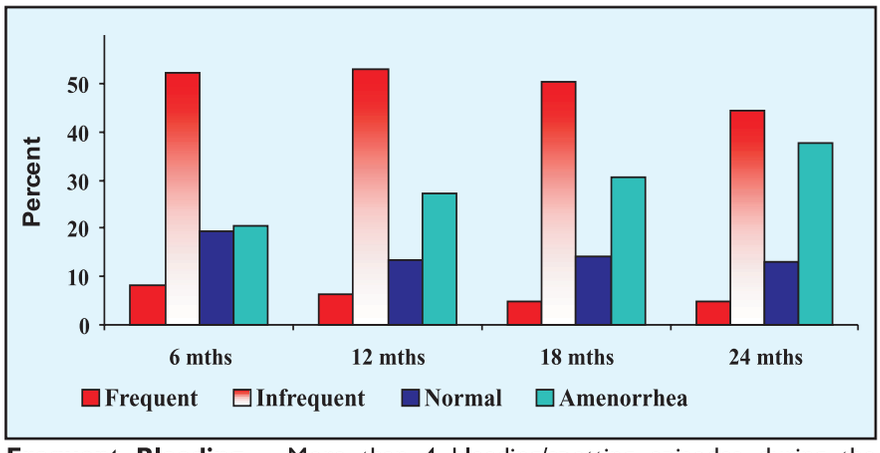


Fig. 2. Docking of OP (red) with FSHα (orange) and FSHβ (blue) and FSHRHB (green) and their active sites indicating the position of H bonds.

Acceptability and Continuation Rates of 2-monthly Injectable Contraceptive Norethisterone Enanthate

In India, there is an unmet need of 13.2% for contraception (NFHS-3), of which about 50% is for birth spacing methods. To reduce unmet need of contraception, the NIRRH, Mumbai has carried out a study towards expanding contraceptive choices. The study focused on issues pertaining to skilled counseling by qualified staff which are very essential for improving acceptability and continuation of injectable contraceptive, norethisterone enanthate. Menstrual pattern among injection users was analyzed (Fig. 3) using a 90 day protocol as per WHO guidelines with modification. A total of 5666 reference periods were studied during a 2-year injection use. Infrequent bleeding pattern was well accepted by women after effective counseling. Based on these findings, Government of India has considered introduction of the injectable contraceptive into the National Programme.



Frequent Bleeding – More than 4 bleeding/spotting episodes during the reference period
Infrequent *Bleeding - 1-2 bleeding or spotting episodes*
Normal Pattern *- 3-4 episodes of bleeding or spotting each lasting about 5-7 days*
Amenorrhea *- No bleeding/spotting days during the reference period*

Fig. 3. Percentages of different menstrual patterns in a two year study period (total reference periods – 5666)

Acceptability and Continuation Rates of 2 Monthly Injectable Contraceptive: Norethisterone Enanthate-Bone Mass Density (BMD) Evaluation by DEXA.

Study was initiated at 6 participating centres where DEXA facility was locally available. Final DEXA scans were done at femoral neck and lumbar spine one year after stopping the Net-En injection among 109 participants. It was observed that mean BMD values were significantly higher among injection discontinuers compared to injection users at two sites (Fig. 4).

No correlation was seen between duration of injection use and mean BMD. There was a positive correlation between body mass index (BMI) and BMD. Women with BMI of 25 and above had significantly higher BMD at both the sites compared to women having low BMI of less than 20. There was inverse correlation between parity and BMD. Mean BMD was significantly higher among women having 1 or 2 children compared with women having 3 or more children. There was no significant difference in mean BMD among injection users compared with control group (Fig. 5).

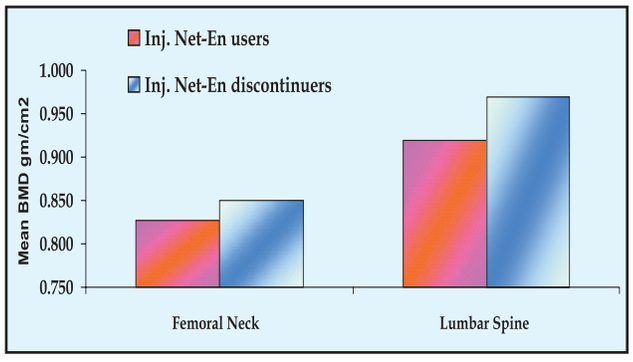


Fig. 4. BMD values by DEXA among injection Net-En users compared with injection discontinuers

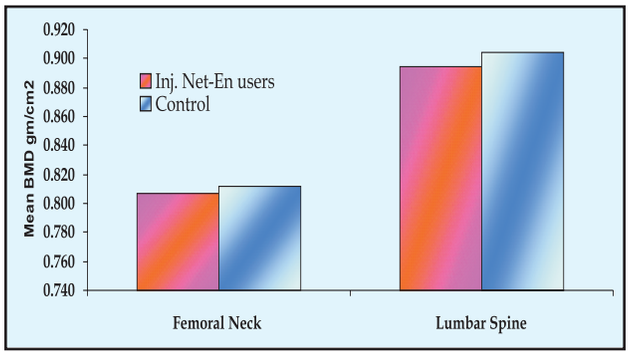


Fig. 5. BMD values by DEXA among injection Net-En users compared with Control

Operational Research

Interventions in Urban Slums for Enhancing Participation of Men in Reproductive Health

Male reproductive health involvement implies encouraging a range of positive reproductive health behaviours in men to help ensure their own well being as well as that of their spouses and children. As a part of the project activity and sustainability of the programme, intervention programmes were carried out for 'husbands only' in experimental area-1 (Mohili Village) and for 'couples' in experimental area-2 (Bail Bazar) by health post staff during April 2008 to December 2008 .

It was observed that after post-intervention survey awareness regarding male and female condom, emergency contraceptive pills and injectables increased significantly in both the experimental areas. Significant increase was also observed in husbands reporting, "vasectomy is better than tubectomy" in both the experimental areas. Significant increase was observed in condom use in both the experimental areas. Proportion of couples making joint decision on number of children in the family increased where couple intervention was provided. Preference for more sons than daughters decreased in both areas. An increase in RTI/STI awareness as well as reporting of RTI/STI symptoms experienced by wives was observed in both the experimental areas.

IEC programmes for couples at community and clinic levels improved health seeking behaviour of both husbands and wives. The number of persons attending the "Clinic for Couples" was comparatively higher than the number of persons attending the "Clinic for Men". Comparatively higher percentage of partners accompanied spouse to avail services at the "Clinic for Men". Pap smear services for screening and detection of cervical cancer and RTIs/STIs at health posts increased attendance of clinics including positive change in health seeking behaviour of couples.

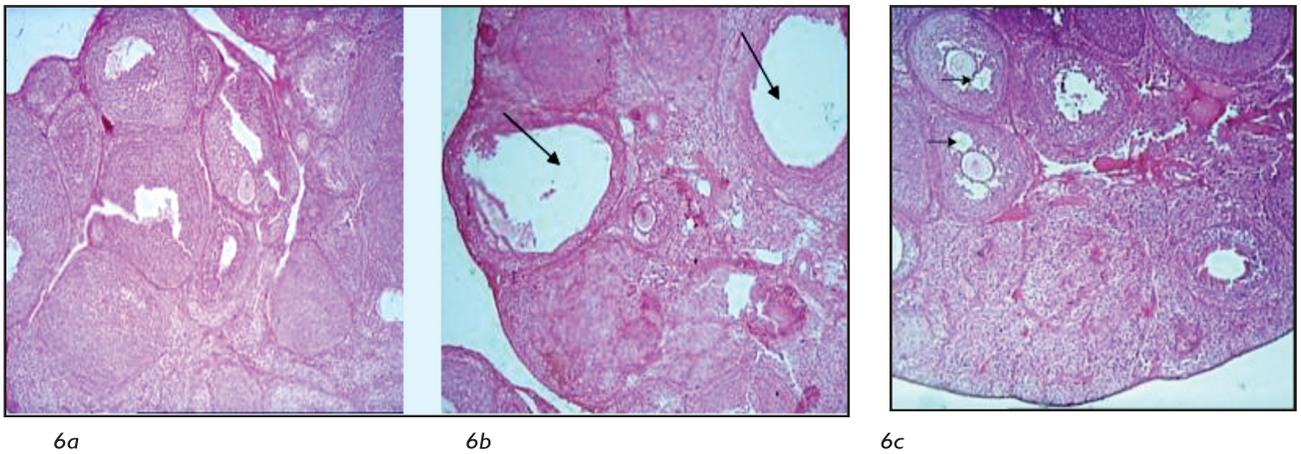
INFERTILITY AND REPRODUCTIVE DISORDERS

Female Infertility

Molecular Studies related to Hyperandrogenemia of Polycystic Ovary Syndrome (PCOS)

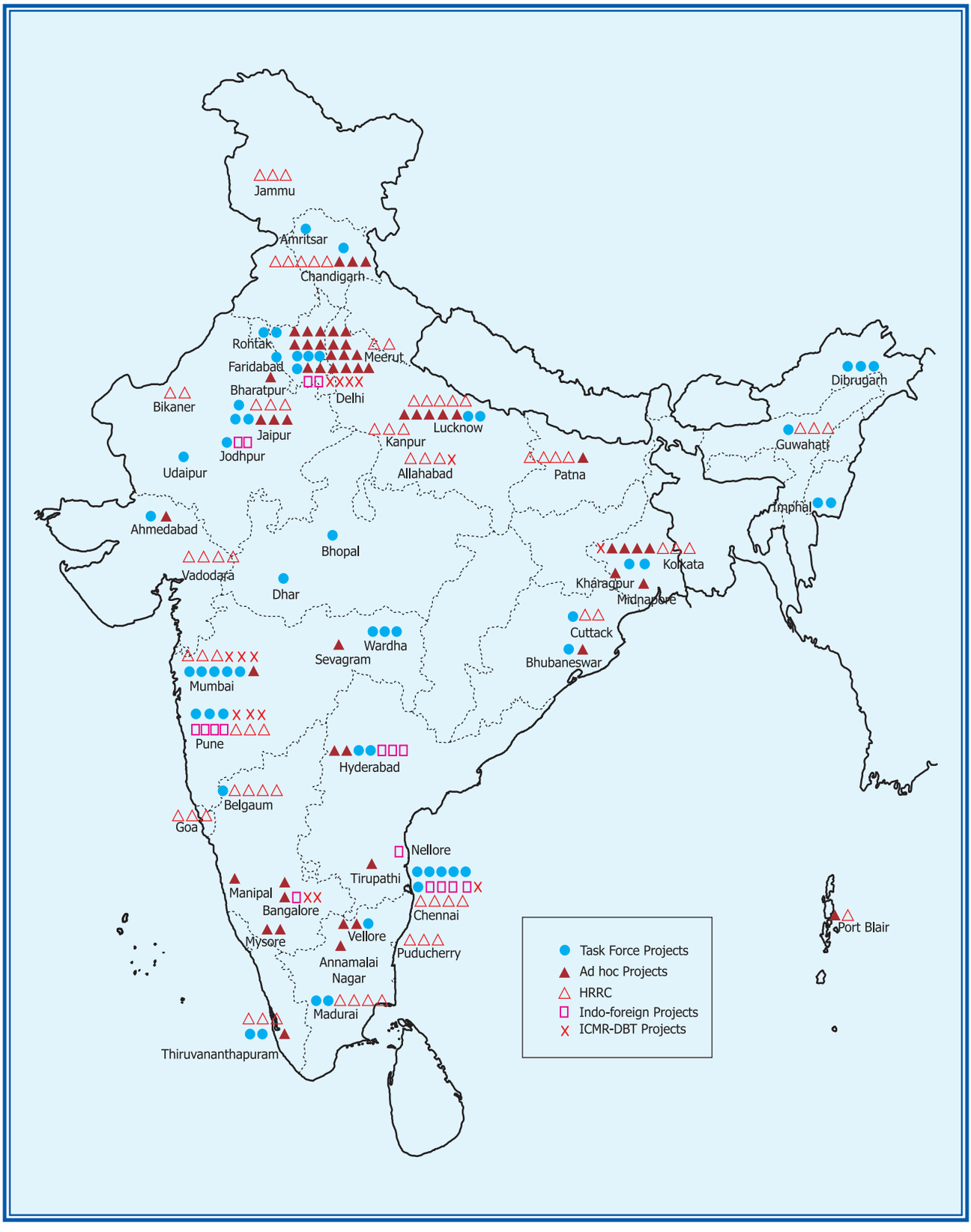
Studies were undertaken using a rat model to elucidate the molecular mechanisms underlying etiology of hyperandrogenemia and hyperinsulinemia. Two main approaches were adopted. First was to develop a rat model in which both these features are manifested. The second approach was *in silico* analysis of the transcriptional regulation of genes involved in PCOS pathophysiology.

The rat model was developed by injecting testosterone propionate (TP) to immature female rats daily for 28 days. Ovaries of rats treated with TP for 2 and 21 days had thickened theca layer as well as large cysts. (Fig.6) Detailed characterization of this model is being carried out at the endocrine, genetic and morphological levels.



6a 6b 6c

Fig. 6. Ovarian histology of control and testosterone propionate (TP) treated rat ovaries. a, b : 2 and 21 days TP treated ovaries showing both thickened theca layer as well as large cysts c: control ovary at 21 days of vehicle (propylene glycol) treatment



Major ICMR Research Projects in Reproductive Health

A software tool called PAINT (Promoter Analysis and Interaction Network Tool) Ver.-3.1 was employed for *in silco* analysis of genes for identification of putative transcription factor binding sites (TFBS). Transcription factors identified include Staf, E47, CCAAT box and CRE-BP1/c-Jun. In all, 71 different transcription factors were identified.

Studies on Genetic Aspects of PCOS

Genetic basis of PCOS is now well recognized, however, genes and genetic variants associated with the syndrome have not yet been identified. A candidate gene analysis was undertaken at NIRRH for determining the genetic mutations / polymorphisms associated with PCOS. Pathway specific genes associated with two major hallmark features of PCOS *viz.* hyperandrogenicity and obesity were investigated. Analysis of promoter region of 3 candidate genes *viz.* CYP11A1, CYP17 and leptin was undertaken. Analysis of CYP11A1 promoter revealed 6 different genotypes in population with 4, 6, 8, 9, 10 and 12 repeats of the (tttta)N pentanucleotide. An association of testosterone levels with higher repeats of the pentanucleotide was also seen. With regard to CYP17, polymorphic C allele was found to be associated with hyperandrogenicity of PCOS. Fig. 7 shows the A>G polymorphisms observed with regard to leptin gene promoter.

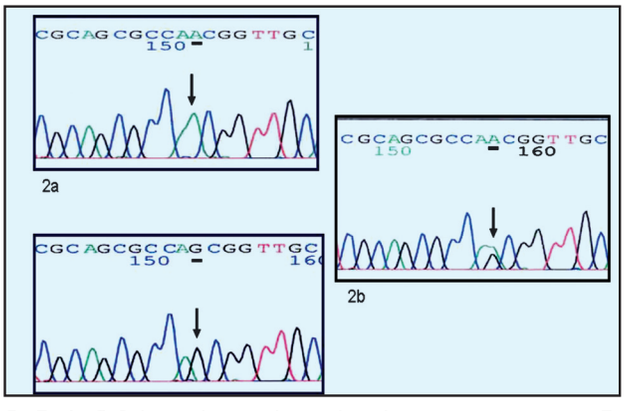


Fig.7. A>G Polymorphisms observed in leptin gene promoter. 7a : Homozygous wild 7b : Heterozygous wild 7c : Homozygous polymorphic.

Genetic Analysis of PCOS with special emphasis on Genes involved in Insulin Resistance

Most of the women with PCOS show insulin resistance, which plays a major pathogenic role. PCOS is a multigenic disorder and the genes related to insulin action have been suggested to be candidate genes for the syndrome. Study was undertaken to determine the role of variants in genes associated with insulin resistance [like insulin receptor gene (*INSR*), insulin receptor substrates, peroxisome proliferator-activated receptor gamma (*PPRγ*), paraoxonase (*PON1*) and ectonucleotide pyrophosphatase phosphodiesterase (*ENPP1*)] in the pathogenesis of PCOS.

A total of 123 women with PCOS were recruited. Genotyping of *INSR, PPRγ* and *PON1* was continued during the year. C/T polymorphism at His 1058 in *INSR* of both PCOS and controls was reported earlier. Further analysis revealed that CC, CT and TT genotypes are not significantly different in PCOS group compared to controls. The polymorphic genotype (CT+TT) showed significant association with PCOS in lean rather than obese women. Lean PCOS women with CT+TT genotype showed significantly increased BMI, waist circumference and fasting insulin.

Regarding *PPRγ* gene, the genotyping at exon B and exon 6 was continued. The frequency of Pro12Ala SNP at exon B which protects insulin sensitivity was not different in control and PCOS women. Genotyping of exon 9 of *PON1* for Q192R polymorphism revealed that there was no difference in the distribution of genotype and allelic frequencies in controls and PCOS.

Genotyping on ENPPI gene at K121Q showed presence of two genotypes AA and AC. The AC genotype is more frequent in PCOS women compared to controls (Fig. 8). The study is in

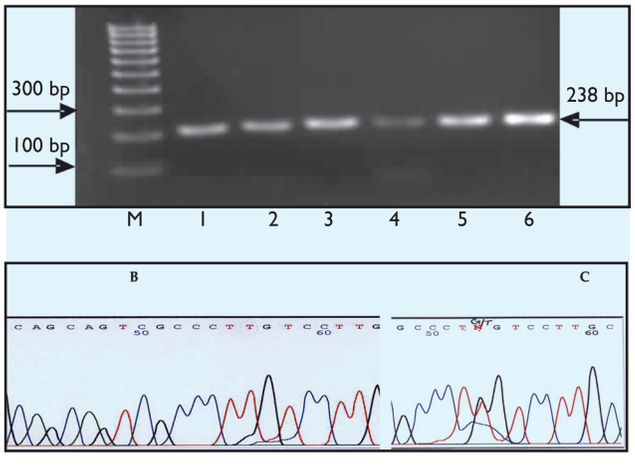


Fig. 8. Amplification of exon 4 of ENPPI gene (A), lane M: 100 bp Ladder; 1 –3: controls and 4-6: PCOS. Sequence of two different genotypes in exon 4 of ENPP1 gene. (B), A/A wild type, (C), A/C heterozygous polymorphic.

progress to analyze the variants of noncoding region of *PON1* and other genes to identify the best candidate gene for PCOS.

Assessment of Gene Mutations Associated with Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by deficiency of one of the five steroidogenic enzymes–21-hydroxylase (21-OH) accounting for about 90-95% of all cases. Study was undertaken with the objective to develop molecular methods for confirmatory diagnosis of CAH, identify the known and novel mutations in 45 index cases of CAH and determine their genotype phenotype association. The types of common mutations observed were Mut.Cd172Ile>Asp (I172>N), Mut.Cd306Tinsert (Tins), Mut.Cd318 Glu>Stop (Q318X), Mut. Cd356Arg>Trp (R356W), Mut.656A,C>G (Intron2 Splice), active gene deletion and exon 6 cluster mutation (Mut.Cd234 Asp>Glu, Mut.Cd237 Val>Glu, Mut Cd239 Met>Lys). Fig. 9 shows some of the common mutations observed. Three novel mutations have also been observed. Functional analysis of these novel mutations is in progress.

Antigens Involved in Ovarian Autoimmunity

Autoimmunity has been reported to be one of the mechanisms involved in pathogenesis of premature ovarian failure (POF) and in *in vitro* fertilization-embryo transfer (IVF-ET) failure cases.

(i) Proteomic Analysis of Ovarian Autoantigenic Repertoire in Infertile Women

Study was undertaken at NIRRH for identifying immunodominant epitopes of antigenic target HSP90β as well as other autoantigenic targets in the ovary. Using antibody epitope prediction tool, 10 immunodominant putative epitopes of human HSP90β were shortlisted and custom synthesized. Of the 10 peptides, EP6 was observed to be the most immunodominant followed by EP1, EP3 and EP8.

(ii) Identification and Characterization of Multiple Autoantigenic Targets in the Ovary

Twenty four percent of the total patients recruited under IVF-ET program tested positive for antiovarian antibodies (AOAs). The dominant target was found to be 90kDa protein (HSP90β)

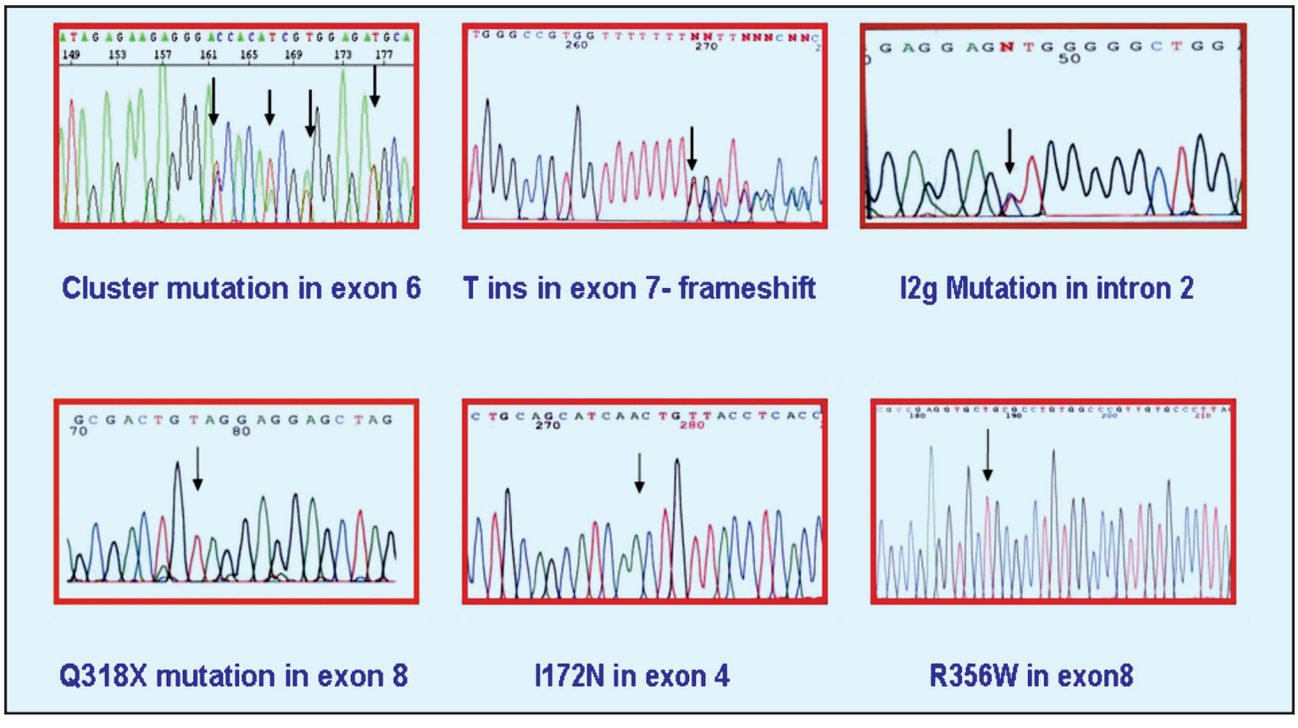


Fig. 9. 21-hydroxylase gene mutations observed in CAH cases. a: Heterozygous C>T substitution in Cd.356 leading to missense mutation Arginine to Tryptophan (R356W). b: Cluster mutation Cd 234 Asp>Lys, Cd 237 Val>Glu and Cd 239 Met>Lys observed in Exon 6.

followed by 97, 80, 120 and 45 kDa antigens which were identified. Immunohistochemical studies revealed that all these antigens were localized mainly in the oocyte, while a few were localized in theca, corpus luteum and zona pellucida. Characterization of these proteins was done at both cellular and biochemical levels. The developmental expression studies indicated the presence of these proteins from birth onwards. The proteins were shown to be well conserved across species. Identification and characterization of these multiple antigenic targets would help in understanding the pathogenesis of the disease and would aid in developing a more specific and sensitive diagnostic assay.

Mechanism of Endometrial Receptivity and Implantation in Primates

Investigations were undertaken at NIRRH to determine whether the expression of calreticulin is hormonally regulated. *In vitro* studies revealed significant upregulation in the expression of calreticulin by estradiol and marginal downregulation by progesterone. Expression of calreticulin and estrogen receptor alpha (ER-α) in endometrium during embryo attachment was studied in pregnant animals and found to be higher as compared to that in non-pregnant animals while that of estrogen receptor beta (ER-β) was not altered in pregnant animals. Two fold increase in expression of ER-α and COX-2 mRNA transcripts in the stromal cells of pregnant animals was seen. Predominance of complement C3 precursor fragment and ferroxidase was also seen in the sera of pregnant animals. The studies show that dramatic alterations occur in the peripheral circulation as well as at tissue level with the initiation of embryo attachment in pregnant animals.

Deciphering the Role of Homeobox Protein HOXA10 in Endometrial Receptivity and Decidualization

Homeobox (HOX) genes are developmental factors that regulate body axis patterning and segmentation during embryogenesis. HOXA10 is involved in differentiation of the uterus during development. Studies conducted at NIRRH during the year revealed that HOXA10 is required to maintain the decidual phenotype in human endometrial stromal cells. To identify the pathways by which HOXA10 maintains the decidual response, analysis of 30,000 genes was performed by microarrays. About 1040 genes belonging to multiple pathways were identified to be differentially expressed upon HOXA10 down-regulation suggesting that this homeodomain gene regulates multiple events in the decidual cells to support embryo implantation and maintain pregnancy.

Male Infertility

Investigation of Functional Proteins relevant to Sperm Motility Using Proteomics and *in silico* Approach

Study was undertaken at NIRRH to identify phosphoproteins involved in sperm motility. So far ten phosphoproteins have been identified of which six were downregulated and four upregulated in sperms of asthenozoospermic males. Study will provide leads for the treatment of asthenozoospermia.

Molecular Characterization of Human Sperm Progesterone Receptor

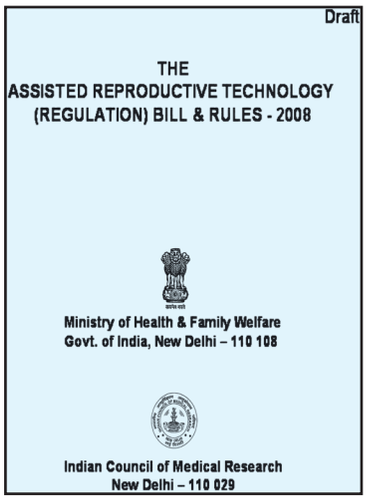
In the reporting year, investigations were undertaken at NIRRH to elucidate the various signal transduction molecules activated in spermatozoa in response to progesterone. The results reveal that progesterone activates multiple kinases in sperm whose activity seems to be temporally regulated in a dose dependent manner.

Characterization of Molecular Events during Spermiation

Spermiation is the final phase of spermatogenesis, whereby mature spermatids are released into the seminiferous tubule lumen. Earlier studies demonstrated spermiation failure in estradiol treated adult rats, thereby causing the spermatids to be retained in the seminiferous epithelium and phagocytosed by the Sertoli cell. The caudal sperm count was also significantly decreased reflecting spermiation failure. Further studies demonstrated that spermiation failure was caused because of absence of the testis specific adheren junctions, namely tubulobulbar complex, involved

in the release of spermatids and effect on Sertoli cell cytoskeleton. Efforts are ongoing to identify proteins involved in spermiation by proteomics approach.

The Assisted Reproductive Technologies (ART) Bill & Regulations - 2008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THE
ASSISTED REPRODUCTIVE TECHNOLOGY
(REGULATION) BILL & RULES - 2008

Ministry of Health & Family Welfare
Govt. of India, New Delhi – 110 108

Indian Council of Medical Research
New Delhi – 110 029

The draft ART Bill & Rules–2008 developed by the Council is being subjected to public debate by placing it on the websites of ICMR and MOHFW with a request for comments from the public. After Parliamentary approval it will become mandatory for all the ART clinics in India to be accredited and maintain all the records as per the Bill and submit to a Central database. The Council has developed a detailed proposal to establish the National Registry of ART Clinics in India at ICMR Hqrs., New Delhi as per recommendations from MOHFW.

REPRODUCTIVE TRACT INFECTIONS

Association of HLA with HIV Infection

Host genetic diversity is believed to contribute to the spectrum of clinical outcomes in different infections. A study was undertaken to investigate the association of host genetic factors (*i.e.* human leucocyte antigen, HLA) with *C. trachomatis* infection leading to different types of manifestations in women. Study revealed significant association of HLA A*33 and HLA DQB1*04 in protecting women from infertility and recurrent spontaneous abortions.

Identification, Purification and Characterization of Antifertility Compounds from Indian Mud Crab, *Scylla serrata*

Attempts were made to produce an antimicrobial peptide (SSP12) from *S. serrata* by recombinant method using *E.coli* expression system. Its efficacy is being tested.

Development of National Training Strategy for Medical Officers, ANMs, and Laboratory Technicians to deliver RTI/STI Services in the Primary Health Care System

During the year the training programme was developed and the modules field-tested at six sites with trainee doctors, ANMs/nurses, and lab technicians. Based on the report of the pilot training, the modules were revised and submitted to the Ministry. The Ministry sent the modules to experts at NIHFW and WHO. The final version of the field tested modules was submitted to NIHFW. The modules were recommended to be used for training in the NACP and RCH programme.

Contraceptive and Sexual Practices among HIV Concordant and Discordant HIV Infected Persons

The HIV infection is increasing among young population. There is a need to counsel these people about barrier contraceptive use and safe sexual practices. A total of 301 HIV infected persons (18-55 yr age) were interviewed; of these true status of HIV positivity about their partners/spouses was revealed by 62.5%. Of these, 91.5% couples were concordant and 8.5% were discordant, while remaining 37.5% did not know the HIV status of their partners since they were not screened.

Preliminary findings reveal that 18% participants were not aware about condom usage for prevention of HIV transmission, however, their wives were using other contraceptive methods for prevention of pregnancy. Seven percent participants said that if both the spouses are HIV positive, there is no need to use condom. No couple had knowledge of emergency contraceptive pill in case of condom breakage/slippage. Majority of the husbands, particularly migrants, do not disclose their HIV positive status to wives and also do not permit their wives to undergo HIV screening test. Even males at high-risk sexual behaviour do not visit voluntary confidential counseling and testing centres because of the fear of HIV positive report and associated social stigma. The observations reveal that skilled counseling by qualified staff about safe sexual and contraceptive practices is necessary to cater to the needs of HIV infected people. HIV services should be integrated into existing family planning clinics.

PRECLINICAL REPRODUCTIVE AND GENETIC TOXICOLOGY

The National Centre for Preclinical Reproductive and Genetic Toxicology has been established at NIRRH, Mumbai. Acute, sub acute and genetic toxicity studies on biodegradable polymer (polyethylene sibacate; PES) as well as on curcumin nanoparticles have been completed. Both these compounds failed to show any target related toxicity or genetic toxicity.

Exposure of Endocrine Disrupter, Bisphenol A (BPA) in Neonatal Rats

The programming of the hypothalamus-pituitary-testicular (HPT) axis as well as development and differentiation of the testis and reproductive tract occurs during neonatal period in rodents. Study was undertaken to investigate the effect of exposure of neonatal male rats to low doses of BPA on their fertility. Amongst the various doses studied, lowest (2.4 µg) dose of BPA could impair fertility in males and neonatal exposure lead to impairment in spermatogenesis during adulthood. Seminiferous tubules showed sloughing of germ cells into the lumen and there was alteration in expression pattern of Sertoli cell junction protein complexes *viz.* N. cadherin, Cx-43 and ZO-1 during development.

OSTEOPOROSIS

Population based Reference Standards of Peak Bone Mineral Density (BMD) of Indian Males and Females

A multi-centric study was undertaken (2001-06) to determine the peak bone mineral density (PBMD) for healthy Indian males and females aged 20-29 yr to revise reference standards. A total of 808 subjects (404 males and 404 females) were enrolled to obtain BMD at the three body-sites namely, total hip, forearm and lumbar spine, mean and 2SD of which were 0.988±0.131, 0.611±0.052 and 0.976±0.105 gm/cm^2 respectively in males and 0.901±0.111, 0.538±0.044 and 0.954±0.095 gm/cm^2 respectively in females.

The estimates obtained in the present study were found to be significantly lower than the corresponding NHANES-III (USA) and HOLOGIC reference standards currently under use. The impact of various demographic, physical (height, weight and BMI), clinical and biochemical factors affecting BMD were also assessed. Amongst the demographic parameters, the nature of physical activity was found to have strong impact on BMD. All the physical parameters had significantly affected BMD with weight alone contributing maximum. Amongst the biochemical parameters, serum albumin, serum alkaline phosphatase, serum vitamin D and serum parathyroid had affected BMD at one site or the other.

Osteoporosis in Men

In women estrogen deficiency associated with ageing is considered an established cause of bone loss. However, normal variability of bone mineral density (BMD) in course of ageing in men is not adequately known. The extent of changes in sex steroid levels with age and its relation to BMD was assessed in healthy Indian men. Studies reveal that there was age-related decrease in bio available sex steroid levels. Amongst sex steroids, Bio-E_2 was found to be an independent predictor of BMD.

STRUCTURAL BIOLOGY

Delineation of the Role of Extracellular Loops of FSH Receptor (FSHR) in Ligand Mediated Signaling

Antibodies to peptides corresponding to extracellular loop (EL) region have been developed and characterized at NIRRH, Mumbai. The antibodies corresponding to EL1 and EL3 were found to inhibit FSH binding. Further, they were able to partially dissociate the hormone from the receptor bound complex indicating partial accessibility of the Els.

MATERNAL HEALTH

Antioxidant Status in Pregnancy Induced Hypertension

To compare the oxidative stress parameters in women with pregnancy induced hypertension (PIH), a total of 124 women with PIH (77 with severe and 47 with mild PIH) were recruited. The

average period of gestation was around 36 weeks. Malondialdehyde (MDA) levels in blood increased and superoxide dismutase (SOD) and glutathione peroxidase activity decreased in women with PIH. Vitamin E and C levels increased significantly in women with mild PIH.

Transfer of Anti-tubercular Drugs from Maternal Circulation to Breast Milk

A study was undertaken to assess the transfer potential of anti- tuberculosis drug (isoniazid, INH) from circulation to breast milk and the factors that may influence its metabolism and transfer to the breast milk. The results indicate that isoniazid is quickly absorbed and transferred to milk in a concentration dependent manner. Genotyping for NAT2 was carried out. Based on these genotypes, the population could be classified as fast, intermediate and slow acetylators. In slow acetylators the concentration time profile graph of INH clearly showed a higher concentration of the drug as compared to fast acetylators.

Relation between Domestic Violence and Poor Maternal and Infant Health

Study was carried out at NIRRH to assess effect of domestic violence (from husbands and other family members) on recent mothers around the time of pregnancy; and determine relation between pregnancy complications and poor maternal and infant health. Preliminary findings reveal that almost half of the women have been abused by husbands either an year before pregnancy, during pregnancy, or immediately after pregnancy. Around 38.5% women were abused by their husbands when pregnant and around 20% reported abuse from in-laws during pregnancy. They were provided counseling and support services by NGO's such as *Dilaasa, Stree Mukti Kendra, etc.*

CHILD HEALTH

Home Based Management of Young Infants (0-60 days)

Under this project extensively trained village level workers called *Shishu Rakshaks* (SR) and *Anganwadi* workers (AWW) delivered intervention in rural areas of five states in the country by conducting survey of eligible women and registering pregnant women at 5th month through house to house survey, three visits during antenatal period for health education, identification of high risk pregnant women and their referral to higher facility. They attended home deliveries with traditional birth attendants (TBAs), provided care at birth including asphyxia management, early initiation and promotion of exclusive breast feeding, early identification of minor illnesses and treatment and identification of serious illnesses and referral to facility and treatment of probable sepsis with oral and injectable antibiotics, if referral is refused. All babies are being followed up for 60 days during postnatal period. Field workers also collected data on key performance indicators. Coverage of intervention is shown in Fig. 10 & 11. Till date

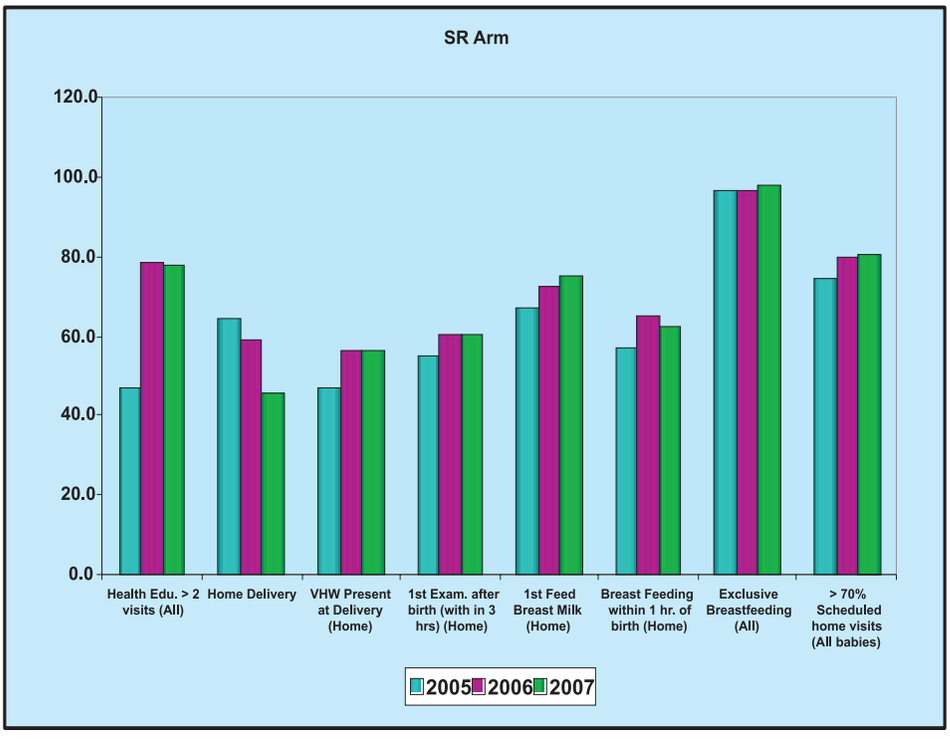


Fig.10. Performance indicators : SR arm

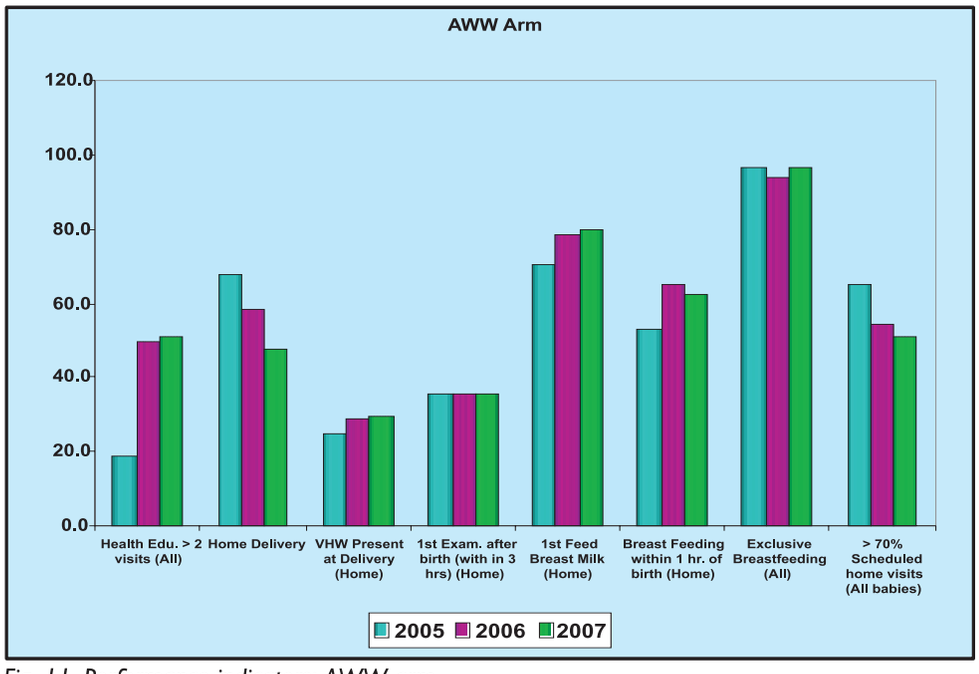


Fig. 11. Performance indicators: AWW arm

more than 1000 probable sepsis cases have been managed by SRs with injection Gentamicin and oral Cotrimoxazole without any serious adverse event. Field activity of the project has been completed.

Pune Low Birth Weight Study – Birth to Adulthood

A cohort of 161 low birth weight children(<2000 gm) born in a tertiary hospital in Pune were followed up till 18 yr of age to study the cognitive problems, potential for learning (scholastic performance) and to determine whether biological and environmental risk factors at birth contribute to the IQ of these children. Socio-economic status and mother's education were found to have a great impact on IQ. Preterm, small for gestation age children from upper middle and higher socio-economic classes had better IQs than those from the lower classes. Very low birth weight (VLBW) (<1500g), preterm and small for gestational age (SGA) children have lower IQs. Development quotient (mental –MeQ) at 1 year had a good correlation with IQ at 18 yr. Preterm females had a smaller head circumference, so also all VLBW children. Preterm SGA children had low scores in mechanical reasoning. All low birth weight children showed poor speed on differential aptitude test. Although full term SGA males had higher systolic and diastolic blood pressure as compared to controls, none were in the hypertensive range hence the SGA males need to be watched closely in future for development of metabolic syndrome.

ADOLESCENT REPRODUCTIVE HEALTH

Improving Service Utilization by Adolescents through Urban Health Posts in Mumbai

A collaborative project was undertaken by NIRRH with the health department of Municipal Corporation of Greater Mumbai (MCGM) with the objective to create an adolescent friendly environment at the urban health posts as well as in the community and improve their service utilization through networking within the existing health care infrastructure.

A post intervention survey in the defined population was undertaken. Analysis of data showed significant improvement in knowledge of adolescent boys and girls about various reproductive health issues. A dissemination meeting on the project performance, challenges and directions ahead was undertaken with the MCGM authorities and health post staff and a plan was worked out for sustenance of the centres Four doctors from MCGM were trained for Adolescent Friendly Health Services and the activities were handed over to the MCGM in March 2009.

Nutrition

The National Institute of Nutrition (NIN), Hyderabad is engaged in community and clinical studies on nutrition, malnutrition and infection, degenerative diseases, food biochemistry and food and drug toxicology.

COMMUNITY STUDIES

National Nutrition Monitoring Bureau

Second repeat surveys by National Nutrition Monitoring Bureau (NNMB) on diet and nutritional status of tribal populations in India gave some insights into time trends. No significant change was observed in the dietary patterns of tribal population in the last three decades. However, consumption of income-elastic foods like pulses, green leafy vegetables (GLVs), sugar and jaggery has marginally gone up. Prevalence of severe undernutrition has significantly come down from 10% to 5% among both the rural and tribal communities. However, there was a notable shift from moderate to mild malnutrition indicating betterment of nutritional status. Nutritional status of tribals of MP, Maharashtra and Orissa was poor compared to that of tribals in other states.

Mid-day Meal Programme for School Children

The bio-effect of ultra-rice on iron status of beneficiaries of mid-day meal programme was evaluated. It was found that rice fortified with iron when given in the mid-day meal to school children for over a year, resulted in significant improvement in their haemoglobin levels and iron stores. However, children in control group who did not receive ultra rice but got supervised meal as per the norms of mid-day meal programme also showed improvement in Hb but no change in iron status.

Assessment of Iodine Deficiency Disorder, Anemia and Nutrition Intervention in School Age Children of Jodhpur

A survey was conducted by DMRC, Jodhpur to study the distribution and magnitude of iodine deficiency disorders and anemia in school children of Jodhpur, for assessment of the extent of use of iodized salt by the community and to study the effect of supplementation on micronutrient deficiency disorders. Discoloration of hair was observed in 42% children and night blindness in 0.4%. Total goiter rate was 5.3%. Stunting was seen in 29% and severe stunting in 7.7 % children. Underweight was observed in 43.1 %. Both stunting and underweight were higher in males than females. Around 28% school age children suffered from mild to moderate iodine deficiency disorder while severe iodine deficiency disorder was observed in 14% children. Iodine content of 470 salt samples was estimated. Overall high proportion of children (72.6 %) consumed salt having inadequate iodine content i.e. less then 15 ppm.

Nutritional Status along with Morbidity and Mortality of Neonates in Jodhpur

Study was carried out at DMRC to assess health and nutritional status of neonates and to find out the causes of morbidity and mortality among them. Preliminary analysis revealed that main morbidities at the time of birth were fever and stomach ache. Mortality was 3.4% due to fever and low birth weight. The percentage of low birth weight babies was 17.8%.

Impact of Daily Zinc Supplementation to Low Birth Weight Infants on Mortality and Severe Disease

Zinc supplementation prevents diarrhoea and pneumonia in 6 month to 3 yr old children. A double blind randomized placebo controlled trial was carried out in 2012 hospital-born infants with a birth weight <2500 g with the objectives to determine the impact of daily zinc administration. Zinc group received 5 mg elemental zinc as acetate daily from 4 weeks age. Number of infants with one or more diarrhoea episodes was reduced by 17% in the zinc group but the number for acute respiratory infections were similar in the two groups. It was observed that hospital born, low birth weight infants do not seem to derive worthwhile benefit from daily zinc supplementation in terms of morbidity and growth during first six months of life.

Nutritional Profile of Population in North-eastern States

A task force study in Assam, Manipur and Meghalaya was carried out to study the nutritional profile of population *viz.* haemoglobin, ferritin, B12 and folic acid levels, sub-clinical vitamin A deficiency (serum retinol level), iodine status (urinary iodine level), zinc and selenium, serum vitamin D, parathormone, calcium, phosphorous and alkaline phosphatase, diet status among children 6-71 months and pregnant mothers. A total of 12,000 blood serum, 5,000 urine and 3,000 salt samples have been collected and analyzed for parameters mentioned above. Statistical analysis is being carried out.

Capacity Building of Primitive Tribes for Health Care

The study is operational in 15 districts of 7 states of the country. Two link persons (One Tribal Welfare Volunteer and one Dai Volunteer) have been identified for every 500 population and trained for treatment of minor ailments and safe delivery respectively. Appropriate kits have also been provided to them. The volunteers are also working for motivating the community to avail nearby health facilities. The study has demonstrated a sustainable model using community.

Body Mass Index (BMI) and Percent Body Fat in Urban Indians

Studies on relationship between body mass index (BMI) and percent body fat in urban adults indicated that cut-off levels of BMI were similar to those for Asian Indians suggested by WHO.

ICMR Validation Laboratory

The laboratory has been set up to act as a referral laboratory for training and external quality maintenance in research work, to take up standardization of appropriate methodologies and to facilitate / carry out need based nutrition research, independently and in collaboration with various medical colleges, research institutes, universities, especially for north east and other inaccessible population of the country. External quality assurance programmes have been undertaken with BIO-RAD, CDC, Atlanta and CMC, Vellore. The Lab is imparting training to lab and field staff.

CLINICAL STUDIES

In a study on lactation related changes in bone mass in women from low socio-economic group, it was observed that women who had better body weights and higher lean body mass were protected from bone loss during lactation in spite of low calcium intake.

A study on relationship of maternal body composition to the birth weight of the infants indicated that the maternal lean body mass and not the fat mass may be the major determinant of birth weight.

When bone parameters of men and women with hip fractures were observed in a hospital based study, it was found that osteoporotic fractures occurred 10-15 years earlier among Indians compared to Western populations.

Studies on maternal and neonatal fat changes in relation to birth weight of infants showed that women who delivered low birth weight babies

were malnourished during pregnancy. Weight gain and fat gains of these women during pregnancy were low and infants had higher neonatal fat percentage.

Studies to find out the antioxidant status among women with preeclamptic toxaemia revealed that antioxidants decreased in all forms of preeclampsia.

NUTRITION AND INFECTION

Immune status / response and its association with leptin status was studied in obese mutant rat models and it was observed that there were altered T cell subsets and B cells in both the sexes of the strains of mutant rats studied. However, the splenic proliferative response to mitogen decreased in male rats of one strain.

Allergenicity evaluation of a bio-preservative skimmed milk fermentate (SMF) which can increase the shelf life of milk products suggested that it had no allergenicity potential in the concentration tested.

BASIC STUDIES

Studies on mechanism of cytoprotective effect of zinc in Caco-2 cell intestinal model indicated that zinc inhibits oxygen induced iron uptake and signaling and thus elicits its cytoprotective effects. This also explains the inhibitive effect of zinc on iron absorption.

In yet another study, enzyme ferric reductase activity has been demonstrated in human milk fraction which explains why iron is better absorbed through human milk (Fig. 1).

DEGENERATIVE DISEASES

Chronic maternal chromium deficiency increased body fat, especially central adiposity in offspring. It altered adipocyte cytokine levels in circulation and lipid metabolism with increased circulating triglycerides and free fatty acid levels. However, it did not alter gene expression. It also caused impaired glucose tolerance and increased insulin secretion. Rehabilitation could partially correct these changes.

Efforts were made to generate a database on phenolic content of plant foods commonly consumed in India and to evaluate their antioxidant activity. Very strong correlation was observed between the phenolic content and free radical scavenging activities indicating that phenolics are significant contributors to the anti-oxidant activity of nuts and oilseeds commonly consumed in India.

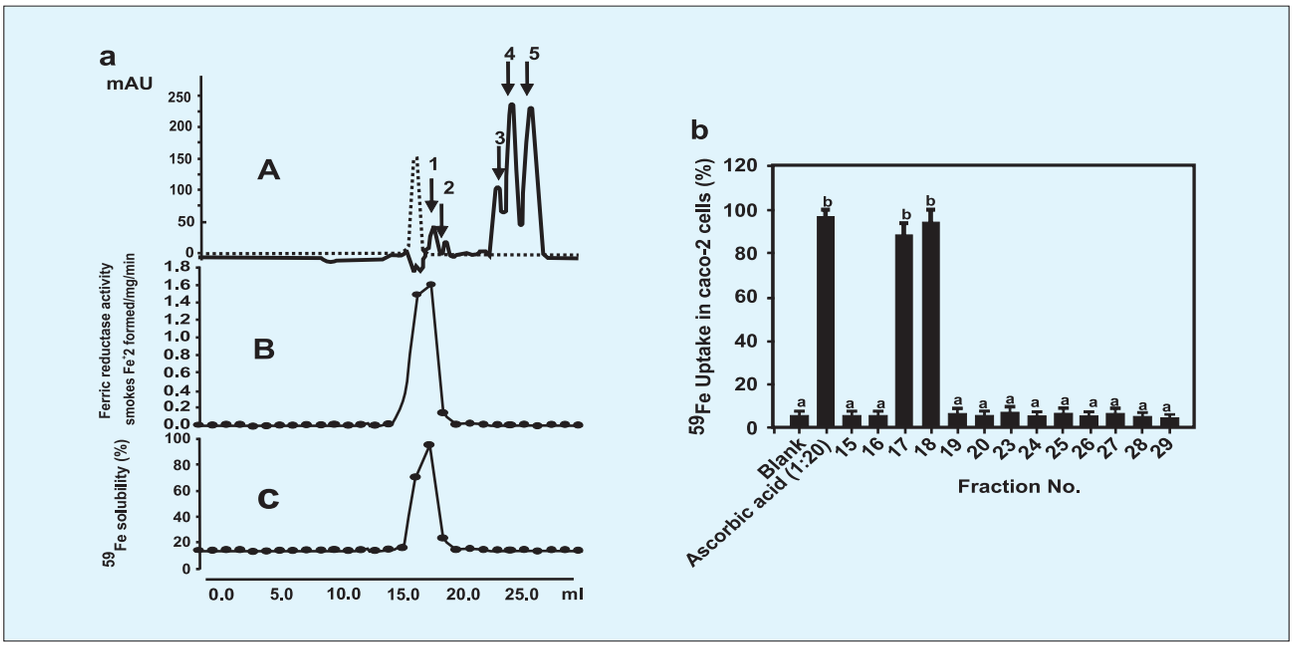


Fig. 1. Identification of ferric reductase activity in human milk associated with enhanced ferric iron uptake in human enterocyte Caco 2 cells. Fractionation of proteins below the molecular weight of cyanocobalmine of 1500 kDa (dotted line, panel A). The arrows 1-5 indicate the peak nos. All the fractions were assayed for ferric reductase activity (panel B), iron solubilization activities (panel C) and uptake of iron in Caco-2 cells (panel D). The bars indicate mean+SD and bars with different letters differ significantly.

MOLECULAR BIOLOGY

A double blind randomized clinical trial has been initiated by NIN as a pilot study to evaluate the role of micronutrients and the impact of supplementation on the disease outcome. The underlying mechanism of functional modulation of macrophages (considered as the first line of host immune defense) by micronutrients is also being examined.

Resistin, a proinflammatory cytokine, earlier implicated to be the link between obesity and diabetes was found to upregulate toll-like receptor (TLR2) expression and hence appears to be a crucial link between TB susceptibility and inflammation.

The NIN is engaged in developing a PCR based quick and easy detection system to identify genetically modified food. Using fluorescence tagged primers, a sensitive multiplex PCR based technique has been developed.

OCULAR BIOCHEMISTRY

Various studies on biochemical, molecular and nutritional aspects of cataract and retinal dystrophies were carried out at NIN. Retinal degeneration in spontaneous obese rat model was discovered. WNIN-Ob rat has opened unique opportunity of using this model for investigating molecular basis and role of nutritional factors in attenuating obesity-associated ocular complications.

Research on functional foods with respect to aldose reductase (ALR2) inhibitors and antiglycating agents has led to the identification of compounds from functional foods as molecular target based adjunct therapies for diabetic complications.

LIPID CHEMISTRY

11β-hydroxysteroid dehydrogenase I(11β HSD1) converts inactive glucocorticoids to active glucocorticoids. Exploration of basal glucocorticoid levels and their possible role in the development of obesity and insulin resistance in WNIN/Ob and WNIN/GR-Ob obese rat model revealed that dietary vitamin A supplementation significantly decreased 11β-HSD 1 activity and its expression in the liver of WNIN/Ob obese rats.

While exploring the potential role of vitamin A and polyunsaturated fatty acids (PUFA) in regulation, development and/or control of obesity in rat models, it was observed that feeding of PUFA rich oil promoted fat redistribution in visceral region, increased functional HDL particles in circulation and improved hepatic steatosis in obese rats.

FOOD CHEMISTRY

NIN has been revising and updating the food composition table on nutritive values of Indian foods. Nutrient database has been prepared for 188 rice cultivars, 43 potato and 20 carrot cultivars. Large variation was observed in protein and mineral content of cultivars.

FOOD AND DRUG TOXICOLOGY

A study carried out on street foods indicated that 50-70% samples of poultry food were contaminated with disease carrying bacteria like *Bacillus cereus* and *Staphylococcus aureus*. The vegetable salads were found to be contaminated with *Salmonella* due to improper handling.

Earlier studies indicated that thiamine can chelate and reduce the uptake of lead in intestines. This was confirmed using *in vitro* human intestinal cell lines. Studies suggest that correcting thiamine deficiency itself would reduce the risk of lead toxicity in populations at risk.

Safety evaluation of a polyherbal drug, AB-FN-02 having potential anti-osteoarthritic activity indicated that it was non-toxic when administered by traditional method with milk and was toxic when administered as a drug otherwise.

Environmental and Occupational Health

The Council's National Institute of Occupational Health (NIOH), Ahmedabad and its Regional Centres at Kolkata and Bangalore carried out a number of studies on occupational health problems of workers engaged in various industries such as silica mills, petrol pumps, *bidi* filling, meat and fish processing and resin manufacturing units *etc*.

Effect of Volatile Organic Compounds on Petrofillers

Occupational exposure of petrol pump workers to monoaromatic hydrocarbons (benzene, toluene, ethylbenzne, o- & m-xylene (combined) & p-xylene, n-propylbenzene and mesitylene) and biological monitoring of the urinary metabolites, (trans, trans – muconic acid, S-phenylmercapturic acid, mercapturic acid, hippuric acid and methylhippuric acid) was studied. Assessment of PM_{10} and its size distribution was done by personal and area sampling techniques.

PM_{10} (particles measuring 10µm or less) exposure in personal samples ranged from 174.5 to 960.4 µg/m^3 and the levels in the outdoor air around petrol pumps were 176.0 – 401.2 µg/m^3. Exposure to toluene was the highest followed by benzene, ethyl benzene, o-xylene, m-& p-xylenes combined, propyl benzene and mesitylene. Increase in levels of all urinary metabolites was noticed in workers exposed to petrol fumes.

Assessment of Feasibility of Dust Control Devices in Small Silica Flour Milling Units

Exposure to crystalline silica produces a lung disease called silicosis and silico-tuberculosis. There are two types of silica mills *viz.* hammer type and ball mill type. At Godhra, (Gujarat) all mills are hammer type whereas at Beawar (Rajasthan) most of the mills are ball type. Exposure to silica dust in ball mills was found to be higher than the permissible level for respirable and total dust. Dust levels in bagging were found to be more than that in feeding of raw materials. A dust control system was designed by NIOH involving hood, ducting, centrifugal fan and bag filters with reverse pulse jet system. MoU was signed with the mill owners at Beawar for installation of dust control system. One hood each was installed at feeding and bagging points (Fig.1). After installation of the dust control system, 89-97% reduction in total dust and 78-85% in respirable dust was found.

Fig. 1. Dust control device

Cold Induced Injuries in Hands of Women Workers

Cold induced dermal injuries, common among workers in occupational groups like meat and fish processing works, cold storages, are characterized by symmetrical intermittent vasospasm of the digital arteries. Study was undertaken at NIOH for assessing cold and wet work induced peripheral circulatory dysfunction by examining the thermographic profiles of fingers and hands of women, on hand and finger skin and categorizing injury pattern temperatures following cold provocation tests (CPT). Women who manifested blanching and Raynaud's phenomena and complained of tingling and numbness in their hands during fish processing activities were subjected to CPT. During CPT, 52% women complained of pain in hand and 22% had unbearable pain in the immersed hand. The delayed CPT recovery group showed significant low temperatures of all the fingers of which middle finger was the most affected. Several women in this group could not at all recover their pre exposure hand temperature even by the 50th min recovery period (Fig.2). The time taken to recover may be considered as the determining factor of cold induced dermal injuries.

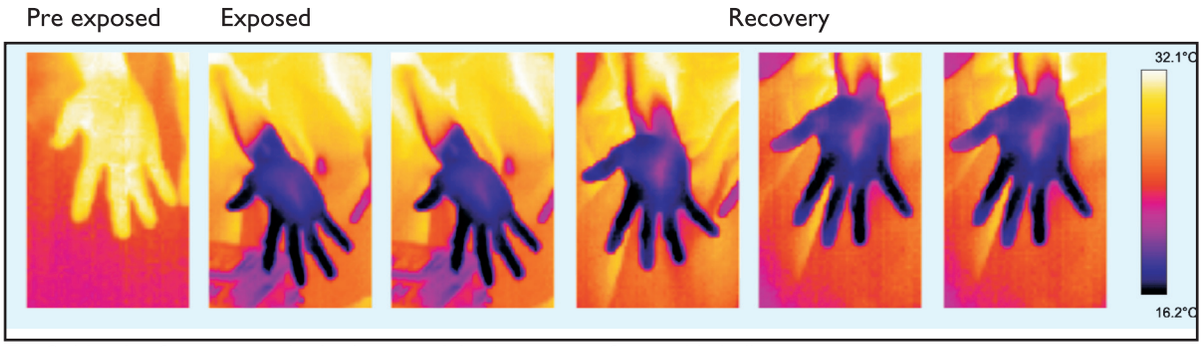


Fig. 2. Hands of a woman who had severe delay in recovery from cold challenge

Assessment of Hazards among Sheep Breeding and Wool Shearing Workers of Karnataka

Sheep farming is a major activity in rural Karnataka. Study was conducted to measure the airborne contaminants during animal handling, shearing and cleaning activities and to quantify the health hazards among workers engaged in sheep farming. The ambient monitoring showed that the average concentration of total suspended particulate matter (TSPM) was 270 µg/m3 in sheep shearing activity. The respirable particulate matter (RSPM) was 237 µg/m3. The RSPM during cleaning of sheds was 148 µg/m3. The shearers were exposed to higher concentration of dust compared to cleaners.

Organic Solvent Exposure and Resulting Health Effects

A study was undertaken in a synthetic resin manufacturing industry where exposure was from organic solvents, mainly formalin. Study was initiated to explore occupational and morbidity details, neurobehavioural and haematological effects and prevalence of hearing loss among workers. Backache, joint pain, headache, respiratory irritation, skin irritation, parosmia, hypertension, obstructive pulmonary function abnormality and hearing loss were observed in workers.

Pro-inflammatory Cytokines and Occupational Health Hazards in Workers involved in Solid Waste Disposal

Study was undertaken at NIOH in solid waste disposal workers to evaluate the relationship between occupational health hazards and serum pro-inflammatory cytokines (IL1-β, IL-6, IL-8, and TNF-α). High levels of respiratory, gastrointestinal, dermatological and musculoskeletal injuries due to contact with sharp objects and heavy equipment were noticed in waste disposal workers. The levels of pro-inflammatory cytokines (serum IL-8, TNF-α) and Ig-E increased significantly in these workers.

Effect of *Pan Masala* on Oral Hard and Soft Tissues

Pan masala chewing might result in oral sub-mucous fibrosis (OSMF), leucoplakia and oral

cancer. Study was undertaken to observe clinical changes in oral hard and soft tissues to study geno and immunotoxic potential of pan masala and to elucidate the role of copper and cytokines in development of OSMF. The results revealed dental attrition and staining in chewers. Oral mucosal lesions were higher among chewers than non-chewers. Serum Zinc levels were reduced in OSMF. Frequency of micronuclei in the buccal mucosa cells of chewers and OSMF subjects was significantly high indicating genotoxic potential of *pan masala.*

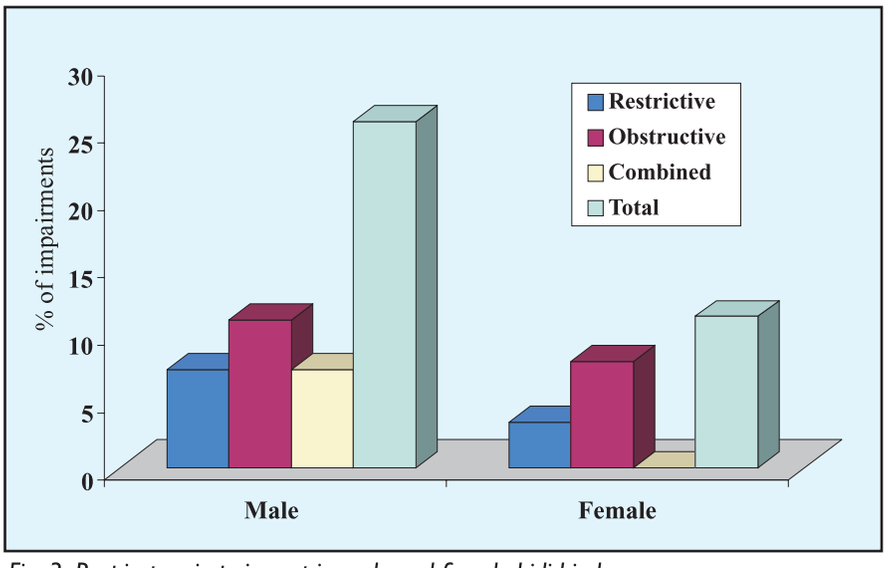


Fig. 3. Respiratory impairment in male and female bidi binders

Respiratory Response to Tobacco Dust Exposure among *Bidi* Binders

Air borne tobacco dust and microbes generated during *bidi* making and processing are the probable risk factors for causing respiratory disorders among workers. Among male and female workers, the prevalence of weakness, chronic diarrhoea and dyspepsia were more in males compared to females. Cough, sputum, chronic bronchitis and breathlessness were the main symptoms; males showing higher rates. Other complaints were pain in neck, low back pain, joint pain, headache, pain in hands and legs and neuropathy. Burning and itching of eyes, conjunctival redness and dimness of vision as well as palpitation were the other complaints. There was high prevalence of nutritional deficiency disorders like anaemia, angular stomatitis and glossitis.

Lung volumes and flow rates of the male *bidi* binders were higher than females. In male *bidi* binders there was gradual decrement of pulmonary function test (PFT) values with increase of age and duration of work exposure. PFT values showed gradual decrement from non-smokers to smokers and smokers to ex-smokers among *bidi* binders. As a whole 25.7% male and 11.2% female *bidi* binders had respiratory function impairments. (Fig. 3)

Assessment of Health Hazards in Arsenic Exposed Population of West Bengal

Consumption of arsenic contaminated drinking water affects multiple systems of the human body. A large number of subjects covering 9 districts of West Bengal are victims of this disorder. Weakness, chronic diarrhoea and dyspepsia were more in arsenic exposed category. The prevalence of cough, breathlessness and chronic bronchitis was significantly higher in males of arsenic exposed category There was high prevalence of musculo-skeletal symptoms like cramps, joint pain (in knee, elbow and shoulder) and neuropathy.

Pallor, angular stomatitis and palpability of liver were more in arsenic exposed population. A substantial number of subjects showed skin pigmentation and keratosis of hands and feet. Definite arsenicosis was noted in males. Exposed population supplied with arsenic free or less arsenic contaminated water for some period of time showed some amelioration in the pigmentary and keratotic changes.

Chromium Exposure and Its Health Effects

A cross-sectional study was carried out to assess the health effects on inhabitants of localities constructed in and around the alleged chromium waste sites. A chromium based chemical industry was closed in the year 2001 and the current health status of the local inhabitants was examined with reference to past toxic exposure. No evidence

of reproductive toxicity was found. No specific health effects secondary to chromium exposure like perforation of nasal septum, dermatitis and spontaneous miscarriage were observed among the local inhabitants.

Environmental Information System (ENVIS)

ENVironmental Information System (ENVIS) at NIOH is engaged in collection, collation, storage, retrieval and dissemination of information related to occupational and environmental health in India. The centre at NIOH is functioning with the objectives of establishment of linkages with all information sources and creation of data bank on selected parameters in the subject area assigned, identification of information gaps, publishing newsletters and bulletins, developing library facility and providing support to the focal point on the subject area and serving as interface for users on the assigned subject.

During the year two newsletters "Endocrine disruptors and Health" and "Arsenic exposure and effects" were published. Two bibliographies containing Indian publications on "Arsenic & Health" and "Lead & Health" have been distributed.

Non-Communicable Diseases

During the year under report, the Council carried out a number of studies on cancer, cardiovascular diseases, neurological disorders, diabetes, mental health, geriatrics, orthopaedics and disability. The National Cancer Registry Project of the Council continues to generate data on various types of cancers in the country. Major intramural research in the field of cancer is being carried out at Council's Institute for Research in Cytology and Preventive Oncology (ICPO) located at NOIDA. The Council is coordinating the project on non-communicable disease surveillance of the Ministry of Health & Family Welfare running in various states of India.

ONCOLOGY

National Cancer Registry Programme

Twenty three population based (PBCR) and five hospital based cancer registries (expanded from previous 11 registries) functioning under the National Cancer Registry Programme (NCRP) of ICMR, are generating reliable data on the magnitude and patterns of cancer; undertaking epidemiologic studies; providing research base for developing appropriate strategies and evaluation of National Cancer Control Programme. They are also developing human resource. Published reports are available till 2005 (till 2006 for north eastern registries). In males, the age adjusted incidence rate (AAR) varied from 49.2 per 100,000 in the rural PBCR at Barshi to 119.5 per 100,000 in the National Capital Territory of Delhi. Among females, the AAR varied from 43.1 per 100,000 in Ahmedabad district to 120.8 per 100,000 in Bangalore. The possibility of a person developing cancer during the life time (0-74 yr age group) was one in eight or 10 people. In the recently initiated registries in north eastern India, Mizoram state (AAR: 191.5 per 100,000 in males, 155.0 per 1,00,000 in females) as a whole and Aizawl district (AAR : 269.0 in males and 208.4 in females) in particular recorded the highest AAR. Kamrup urban district (AAR: 180.5 in males and 131.6 in females) of Assam follows closely in having such high incidence rates. Cancer atlas project is also collecting data in north eastern India to assess minimum cancer occurrence. A study on trends in incidence rates over time from 1982 to 2005 has been completed and the report is under print. Among males, cancers of the prostate, colon, rectum and liver showed significant increase in incidence rates. Among women, cancers of the breast, corpus uteri, ovary, thyroid, gall bladder and lung have shown a rise. Cancer cervix recorded a decline in incidence rates across all registries including rural registry at Barshi. The study on patterns of care and survival aims to collect data on treatment of cancers of cervix, breast and head and neck.

Cancer Screening

A model for screening for cancers of cervix, breast and oral cavity was developed for three districts of Himachal Pradesh. The model components included finalization of strategy, development of manuals and health education aids, baseline survey, infrastructure strengthening and training of professionals and para-professionals.

Review of Cancer Management Guidelines

A task force on review of cancer management guidelines constituted 20 sub-committees to study the guidelines for 20 cancer sites. Guidelines for chronic myeloid leukaemia and buccal mucosa

cancer have been finalized. The draft guidelines on stomach, cervix and lung cancer are being finalized.

Operational Research on HPV Vaccine

ICMR in collaboration with PATH is working on a project to understand the health services requirements for possible HPV vaccine introduction. The formative phase adopted qualitative approaches to assess the preparedness of health services and to plan a strategy for HPV vaccination.

Cervical Cancer

ICPO has been involved in conducting multidisciplinary studies for control of cervical cancer. During 2008-09 this work was continued along the leads obtained in the past. ICPO pioneered the strategy of visual inspection for early detection of cervical cancer. The test characteristics of this modality were compared with that of cytology and HPV screening in the past in a hospital setting. Now efforts have been initiated to carry out such studies in the community. Two new community based projects have been formulated : one for the control of cervical cancer using three alternative strategies in the rural community of Dadri, Gautam Budh Nagar. The screening will be carried out in 10,000 women in the age range of 30-59 yr utilizing trained paramedical workers. Another community based project is a multicentric demonstration project for testing fast HPV (CARE HPV) kits.

ICPO has been selected as one of the sites for carrying out the HPV vaccine trial (Gardasil trial, MERC). During the year under report different formalities for the site selection and site preparation were undertaken.

The Institute was also involved in carrying out a randomized, multicentric trial for clearance of HPV infection in uterine cervix by *Basant* (a polyherbal cream) and curcumin soft gelatine capsules in females infected with HPV.

Studies are also ongoing on SNP profling of immunomodulatory genes in cancer. The Institute was also engaged in development of DNA vaccines against HPV and SNP analysis of cell cycle regulatory genes in cancer.

Other studies ongoing at ICPO include molecular oncologic aspects such as expression profiling and identification of genes associated with development of cervical cancer, analysis of promoter methylation of E-cadherin gene in cervical cancer among Indian women, role of AP-1 and NF-kB in regulation of telomerase activity in cervical cancer cells, transcriptional targeting of human papillomavirus gene expression by herbal derivatives, role of transcription factors, signal transducer and activator of transcription 3 (stat 3) in cervical carcinogenesis.

ICPO has been identified as one of the regional HPV laboratories for monitoring HPV vaccine programme in South East Asia region under global HPV laboratory network (HPV labnet of WHO). Capability has been developed for performing in-house qualitative and quantitative PCR for HPV 16 and 18.

CARDIOVASCULAR DISEASES

Jai Vigyan Mission Mode Project on Community Control of RF/RHD

A study on blood pressure, height and weight measurements was initiated in children aged 5 to 14 yr as a part of *Jai Vigyan* project on RF/RHD. The six centres (Chandigarh, Vellore, Kochi, Indore, Wayanad and Shimla) have collected data on anthropometric and blood pressure measurements in around 70,000 school children. The satellite registries at Jammu, Dibrugarh and Mumbai are undertaking the study in 10,000 children.

Angiotensin Converting Enzyme (ACE) Insertion Deletion Gene Polymorphism in North-east Region

The hospital based case-control study on role of ACE insertion/deletion gene polymorphism in the development of ischaemic stroke and acute myocardial infarction (AMI) continued at RMRC, Dibrugarh. Distribution of ACE insertion-deletion gene polymorphism revealed higher prevalence of D/D (58.3%) and I/D

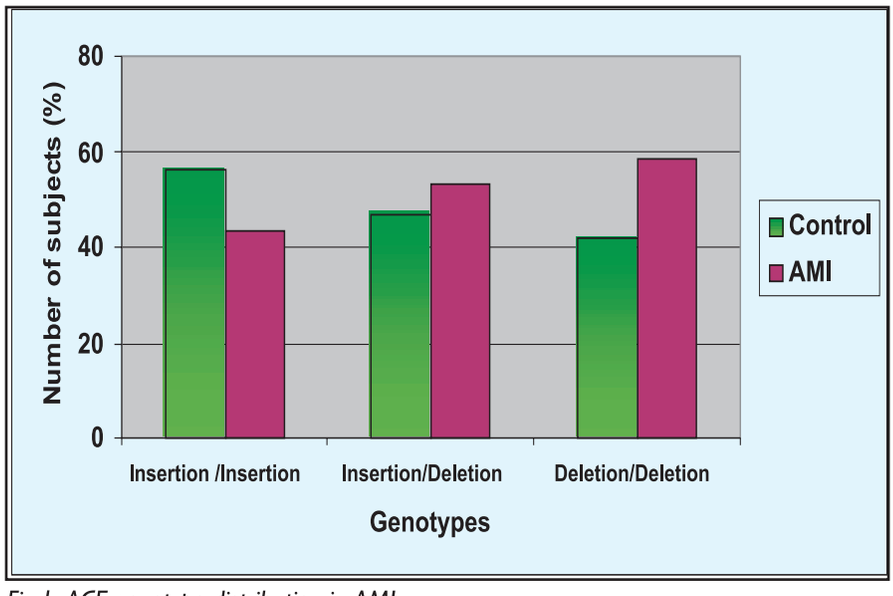


Fig.1. ACE genotype distribution in AMI

(53.3%) and lower of I/I genotype (43.4%) among 312 AMI cases (Fig.1).

Salt Sensitivity and Candidate Gene Polymorphism in Hypertension

A multicentric project on salt sensitivity and candidate gene polymorphism in essential hypertension in tribal population of Mizoram tea garden communities of Assam and indigenous Assamese population was completed in 2008. Salt sensitivity phenotype was observed to be high in hypertensives in both tea garden workers and Assamese indigenous population. Hypertensive subjects with salt sensitivity had higher prevalence of Del/Del genotype in ACE gene in tea garden workers.

Congenital Heart Disease in Children

A pilot project on creation and evaluation of clinical strategy to screen for congenital heart disease (CHD) in newborn was undertaken. The overall prevalence of CHD was high (7.75%). The major finding of the project is extremely low sensitivity of clinical methods for picking up CHD in the first 48 h of life.

Prevalence of Hypertension in Nicobarese Tribals

A study was undertaken by RMRC, Port Blair to estimate the prevalence of hypertension among aboriginal Nicobarese tribe living in Car Nicobar Island and to find out the association with established risk factors of hypertension. The prevalence of hypertension was alarmingly high at 66% while that of overweight/obesity was 35%. This is the first study which highlights the prevalence of hypertension and overweight/obesity among Nicobarese tribe.

NEUROLOGICAL SCIENCES

Epilepsy

Collection of data at registry of epilepsy in pregnancy at Thiruvananthapuram was completed. Malformations were observed in 11.7% and 3.3% of pregnancies with and without epilepsy respectively. A large percentage of malformations in pregnancies with epilepsy as compared to those without epilepsy were cardiac. Also women with epilepsy who were on anti epileptic drugs (AEDs) and polytherapy were at higher risk of malformations.

Stroke

In a study on contribution of prothrombotic state to the etiology of ischemic stroke in the young, majority of the patients had multiple risk factors with large infarcts (in 40.7% of the cases). The homocysteine levels correlated with vitamin B12 levels.

In a study on contribution of prothrombotic state to the etiology of ischemic stroke in the young, the stroke subtype was mainly of anterior circulation. Protein S deficiency was the commonest deficiency (37.2%) followed by protein C deficiency (10%).

A prospective longitudinal study of stroke in Kolkata is ongoing with the aim to determine the natural course and outcome of the stroke patients and to measure the impact of economic and psychological burden on the family members of stroke sufferers. The incidence rate of stroke/100,000/year was observed to be 143.84 in 2003 and 91.26 in 2007.

The 30 day fatality rate was higher in men than in women. Dementia was observed in 12.93% of stroke survivors.

Neuroprotection in Early Life

A project on spatio-temporal expression of Scaffold matrix attachment region (SMAR I) in the developing central nervous system has been completed. SMAR I was found to be strongly and ubiquitously expressed from very early stages of embryonic brain development. The protein may have a role in controlling natural death of neurons and in stress mediated cell death.

DIABETES

ICMR's Centre for Advanced Research

ICMR has initiated a Centre for Advanced Research at Madras Diabetes Research Foundation, Chennai. Two–projects study of genes related to maturity onset diabetes of the young (MODY) and early onset diabetes, and study of genes implicated in ion channel dysfunction in diabetes, were initiated. The entire coding region and the exon-intron boundaries of HNF1A gene are being sequenced. The genotyping was performed for Val255Met polymorphism of HNF4 α gene. The frequency of GA and AA genotypes was found to be significantly lower in MODY and late onset type 2 subjects compared to subjects with normal glucose tolerance. Studies on the genetic variability in KIR6.2 and SUR genes are underway in type 2 diabetes and neonatal samples.

Genomics of Type I Diabetes

The task force project on genomic analysis of major histocompatibility complex (MHC) genes (HLA and non HLA) in type I diabetes in the Indian population is ongoing at three centres *viz* AIIMS, New Delhi; Shere-I-Kashmir Institute of Medical Sciences, Srinagar and Madras Diabetes Research Foundation, Chennai. It aims to do genomic characterization of multiple autoimmune favoring HLA-DR3 haplotypes in type I diabetes (T1D) in different ethnic groups of India (North, South and Kashmiri populations of India) and their comparison with similar haplotypes in Caucasians and to perform extensive sequencing of HLA-C and MICA genes in disease associated haplotypes. Of the various HLA-DRB1 alleles studied, the frequency of DRB1*03 was higher in patients compared to healthy controls (76% *vs* 13.9%). A moderate increase in DRB1*09 was also observed in T1D. On the other hand, HLA-DRB1*15 and DRB1*11 showed protective effect with decreased frequencies in patients as compared to healthy controls.

Registry of People with Diabetes with Young Age at Onset

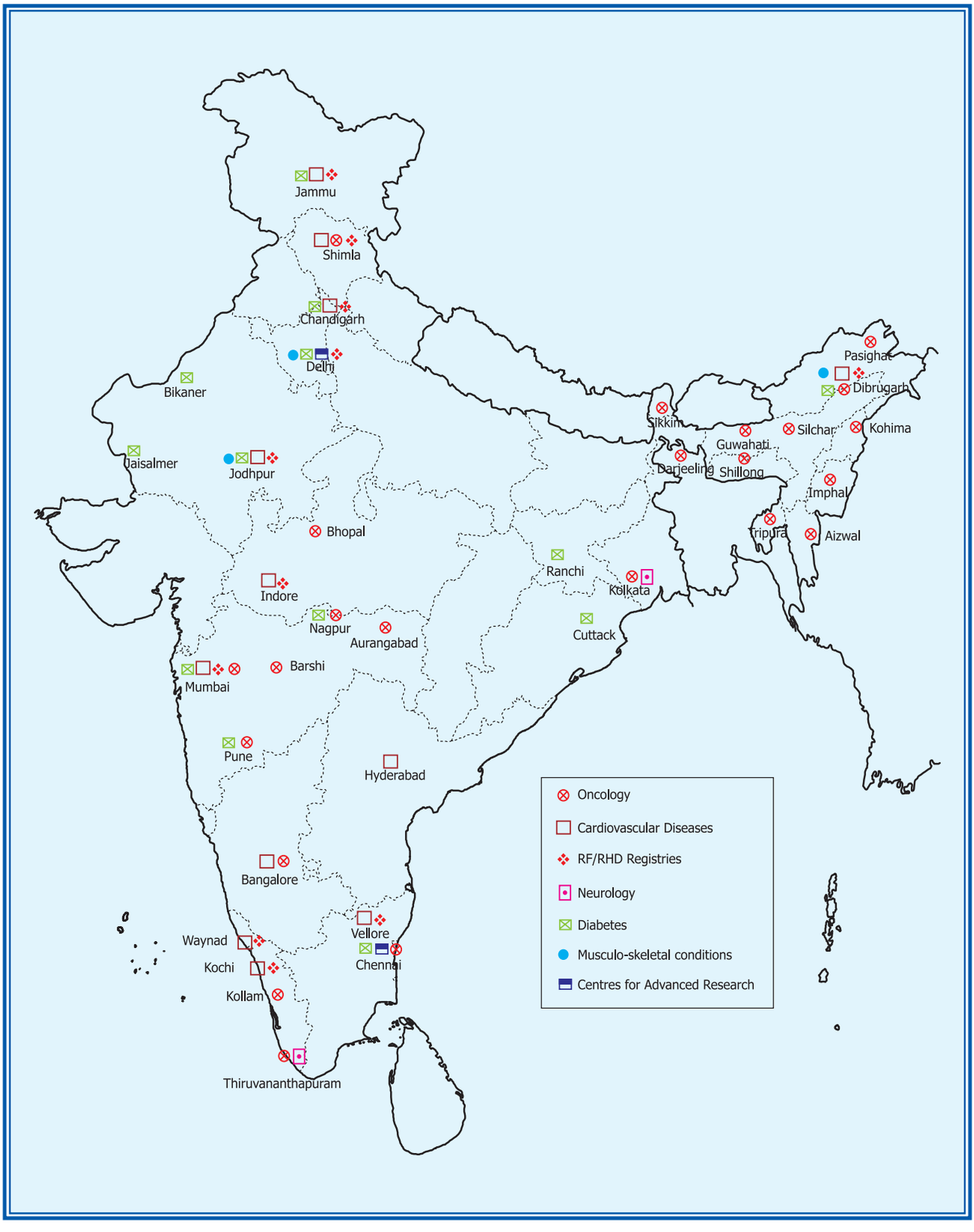
The task force project on "Registry of People with Diabetes in India with Young Age at Onset," is continuing at eight centres with the aim to understand the magnitude of problem, disease pattern or types including the geographic variation and incidence and prevalence of complications. Besides baseline data, the follow up data collection has been started at some centres. The training workshops for filling up proforma of participating centres were held at New Delhi and Chennai.

ICMR-Indian National Diabetes Study (ICMR-INDIAB)-Phase I

A project on ICMR's Indian National Diabetes Study was initiated in 2008 to determine the prevalence of diabetes and pre-diabetes in India, to validate Indian diabetes risk score [IDRS] and to determine normal distribution of lipid parameters at the national level, to assess the association of some known candidate as well as novel genes with diabetes in Indians and study the prevalence of micro-vascular (diabetic retinopathy and nephropathy) and macro-vascular complications (coronary artery disease) in self-reported diabetic subjects. The study will survey 32,000 individuals from 3 states and 1 Union Territory in the mainland of India (Chandigarh, Tamil Nadu, Maharashtra, and Jharkhand). A stratified multi-stage design, similar to the National Family Health Survey - 3 is being followed in this study.

Dermatoglyphic Patterns in Diabetes Mellitus

Dermatoglyphic data from right and left hands of 40 type 2 diabetes mellitus cases from registered Mathur families revealed reduced frequency of



Major ICMR Research Projects in Non-Communicable Diseases

whorls and higher frequency of loops among female diabetics. Frequency of whorl is highly reduced in 3rd fingertip of right hand of male and female diabetics as compared to the loops indicating lesser ridge count on the 3rd finger of the right hand of the diabetics. Family history of Mathur Families revealed that 64.8% were positive for type 2 diabetes.

MENTAL HEALTH

Urban Mental Health Problems and Service Needs

The task force study on urban mental health problems and service needs is being carried out at Delhi, Chennai and Lucknow. It aims to develop a feasible mental health service delivery module for common mental disorders (CMDs) and stress related problems through primary health care providers and to develop an intervention module for victims of domestic violence. The comparison of the findings of lower with middle and higher socio-economic strata (SES) has been carried out at all three sites. Psychiatric morbidity was found to be higher in lower socio-economic groups. Similarly, CMDs were also higher in lower SES as compared to higher and middle SES.

Mental Health Service Needs and Service Delivery Models in Earthquake affected Population in Gujarat

A task force study on mental health service needs and service delivery models in the disaster (earthquakes) affected population in Gujarat is being carried out. The prevalence of psychiatric morbidity was found higher in affected group (61.35/1000) as compared to control group (22.29/1000) in medium affected areas around Ahmedabad. The most prevalent psychiatric morbidities were depressive and recurrent depressive disorders, followed by anxiety, dissociative (conversion) and somatoform disorders in both groups. Similarly, the prevalence of psychiatric morbidity was higher (67.04/1000) in the affected group as compared to control group (22.93/1000) in mildly affected areas in Rajkot. The data from severely affected areas of Bhuj is being analysed.

Mental Health Needs of Tsunami affected Population in Tamil Nadu

A long term study has been initiated on mental health needs assessment and service delivery models in tsunami affected population of coastal Tamil Nadu in two centres at Chennai and Nagapattinam.

GERIATRICS

Determinants of Functional Status of the Indian Older

Looking at the importance of the physical health, a task force project on determinants of the functional status of the Indian older people has been initiated at two centres in Delhi.

ORTHOPAEDICS & DISABILITY

A multi-centric epidemiological-cum-prevalence study was initiated in 2007 to assess the magnitude and impact of select musculoskeletal disorders in adults (age>18 yr) in the community with a focus on osteoarthritis, rheumatoid arthritis and spinal disorders. The study is being carried out at three centres *viz*. Delhi, Jodhpur and Dibrugarh for a period of two years. Ten thousand adult persons are being covered at each centre comprising 5000 each from rural and urban areas. The screening of study population at each centre is nearing completion and confirmation of all screened positive cases and 10% screened negative cases is underway.

NON-COMMUNICABLE DISEASE SURVEILLANCE

On behalf of the Ministry of Health and Family Welfare, Government of India, ICMR was invited to coordinate the implementation of the noncommunicable disease risk factor surveys under the Integrated Disease Surveillance Project (IDSP) in 29 States/UTs over a period of 3 years beginning 2007. The first phase of the survey has been completed in 7 states (Kerala, Tamil Nadu, Mizoram, Uttaranchal, Maharashtra, Madhya Pradesh and Andhra Pradesh) and the reports are being finalized in consultation with IDSP/MoHFW for dissemination.

Basic Medical Sciences

Intramural research activities of the Council are ongoing at the Institute of Pathology (IOP), New Delhi and National Institute of Immunohaematology (NIIH), Mumbai. During the year under report, pathology of various types of cancer and infectious diseases such as chlamydiasis and leishmaniasis were carried out at IOP. At NIIH, studies were conducted on β-thalassaemia, leucocyte biology, leukaemia, characterization of ABO blood groups and aplastic anaemia. Studies were also carried out on haemoglobinopathies in tribals of various regions of the country by RMRCs of the Council. Extramural research projects were continued in the fields of biochemistry, cell and molecular biology, genomics and molecular medicine, pharmacology and traditional medicine in different medical colleges and research institutes of the country. Stem cell research is going on at IOP, NIRRH and other centres in the country.

PATHOLOGY

TUMOUR BIOLOGY

Breast Cancer

One breast cancer cell line (PCB20) has been established from an early onset breast cancer case as an important tool to study molecular carcinogenesis. (Fig.1)

Gene expression profile has been studied in ten cases and role of promoter hypermethylation in five cases of early onset breast cancer using microarray technology to understand its molecular pathogenesis.

Correlation of expression of type I growth factor receptor genes EGFR, c-erbB-2, c-erbB-3 and MDR1 and AR genes in locally advanced breast cancer cases with response to neo-adjuvant

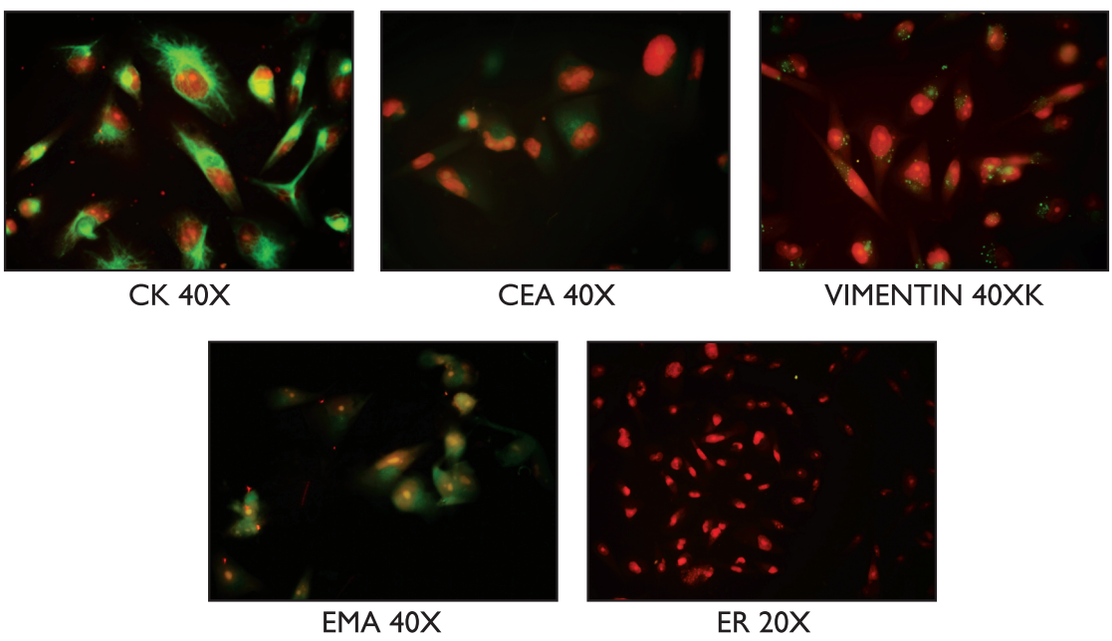


Fig. 1. Expression of biological markers in PCB 20 cell line

chemotherapy showed that AR gene carries independent predictive role.

Urogenital Malignancies

Study to identify CAG microsatellite repeats in androgen receptor gene, (TTTA) repeat analysis in *CYP19* gene, polymorphism in prostate specific antigen (PSA) gene and MLH1 gene in prostate cancer and their correlation with genetic susceptibility and progression of carcinoma showed protective role of GG genotype of PSA gene, slight association of genotype A2A2 of *CYP19* [TTTA] repeat with cancer prostate (CaP) cases and significant association of CC genotype at -93 position of the core promoter region of *MLH1* gene with risk of prostate carcinoma. (Fig. 2)

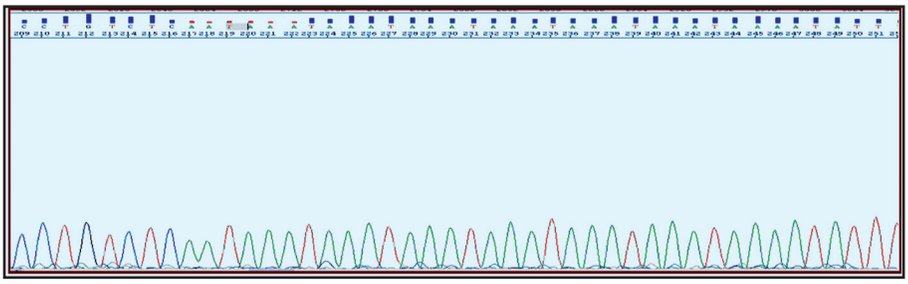


Fig. 2. Electrogram showing the CYP19 [TTTA] repeat in one of the CaP case with the repeat length of 7.

Study on role of effector function of cyclooxygenases (Cox-1 and Cox-2) and associated cytokines in peripheral blood mononuclear cells (PBMCs) in invasive and non invasive transitional cell carcinoma (TCC) of urinary bladder showed increased Cox-2 expression in invasive cancer patients. Significant variation in IL-1B and IL-6 level was observed in patients in comparison to normal group. The expression of CD74 was also found high in cancerous patients compared to controls. (Fig.3)

Cancer in North-East Region of India

A comprehensive study on oesophageal carcinoma to investigate genetic factors associated with tobacco and familial association has been completed. On the basis of gene ontology, four molecular functional pathways (MAPK, G-protein coupled receptor family, ion transport activity and serine or threonine kinase activity) were upregulated and six pathways (structural constituent of ribosome, endopeptidase inhibitor activity, structural constituents of cytoskeleton, antioxidant activity, acyl group transferase activity, eukaryotic translation elongation factor activity) were downregulated in tobacco associated oesophageal cancer. Genes involved in humoral immune response, extracellular matrix organization, metabolism of xenobiotics, TGF-ß signaling and calcium signaling pathways were down-regulated and genes involved in regulation of actin cytoskeleton, neuroactive ligand receptor interaction, toll-like receptors, B-cell receptors and insulin signaling pathways were up-regulated. Validation of differential expression of subset of genes by PCR and tissue microarray in familial and non-familial cases showed no significant difference in expression of these genes in two groups.

No significant contribution of GSTM1 and GSTT1 null polymorphisms was found in oral and gastric cancers. Polymorphism in codon 72 of p53 gene showed that genotype pro/arg may act as a risk factor for gastric cancer while genotype pro/pro acts as protective factor for lung cancer. Gene expression

Fig. A. Fig. B.

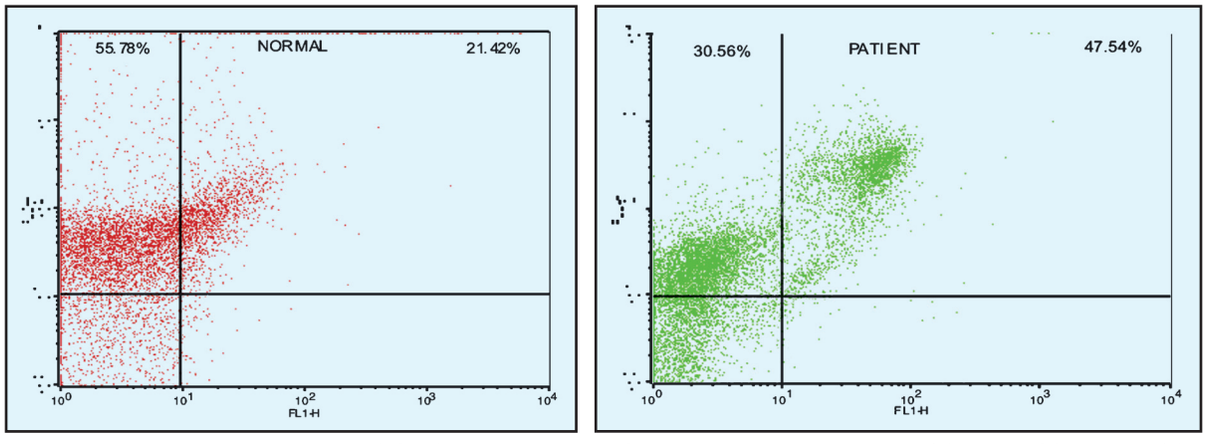


Fig. 3. Dot plots showing the expression of Cox-2 and IL-6 in PBMCs in normal healthy individual (A) and TCC patients. (B)

studies have been initiated in oral, gastric and lung cancers and copy number analysis has been done in oesophageal cancer using 10K array.

In pesticide associated cancers no significant contribution of mutations in BRCA1 and 2 genes, CYP17 and p53 gene and codon 72 polymorphisms have been found, however, GSTP1 null polymorphisms show significant contribution to risk of breast cancer. Copy number analysis by microarray is being done to identify genes associated with risk and progression of breast cancer.

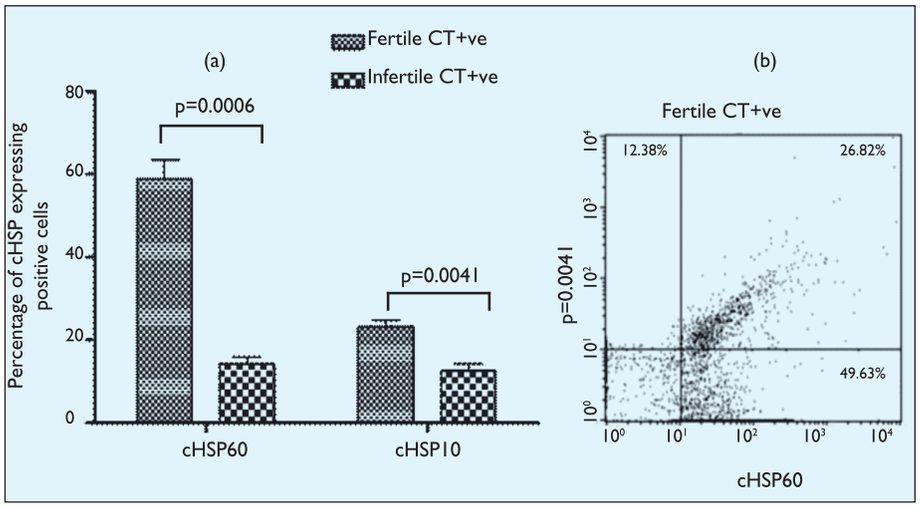


Fig. 4. Flow cytometric assay targeting intracellular levels of cHSP60 and cHSP10 in C. trachomatis infected cervical epithelial cells from each of the seven fertile and seven infertile women. Cells were simultaneously stained with monoclonal antibodies of cHSP60 and cHSP10 conjugated with FITC and PE respectively. Data shown were calculated as mean of percent cell population in each group. Appropriate isotype-matched control antibodies were used to rule out non-specific fluorescence. (a) Percentage of cells stained with either cHSP60 or cHSP10. Bars represent standard error. (b) Representative figure (dot plot) showing intracellular levels of cHSP60 and cHSP10 in infected cervical epithelial cells of fertile women.

Hematopoietic-Lymphoid Malignancies

Study on prevalence and prognostic value of gene mutations in acute myeloid leukaemia (AML) done at IOP showed alterations in FLT3 gene in 23% patients, however, there was no significant difference in response to induction therapy in patients with or without FLT3/ITD mutation. Significant difference in expression of IkB-α, IKK-B, P53, cIAP-2 and survivin was seen in samples of AML and acute lymphoid leukaemia (ALL). Significanly low expression of p53 was found in non-responder group of AML patients which correlated with IKK-alpha gene expression. Expression level of cIAP-2 was significantly lower in non-responder group of ALL patients.

Brain Tumours

A high-throughput tissue microarray (TMA) chip containing 300 brain tumours from archival paraffin blocks has been constructed and used to study the protein expression of differentially expressed genes.

PATHOLOGY OF INFECTIOUS DISEASES

Chlamydiasis

Study on role of chlamydial heat shock proteins in pathogenesis of genital tract infection in women showed that in cervical epithelial cells, cHSP60 and cHSP10 had a different pattern of expression in infertile compared to fertile women. The results strongly support their involvement in immunopathological conditions associated with infertility (Fig. 4).

Study on correlation of chlamydial infectious load with immune factors showed significantly higher inclusion counts in chlamydia-positive fertile women compared to women with fertility disorders with lower recovery of chlamydia from the cervix of these women . Further, chlamydial inclusion forming units (IFUs) correlated positively with CD8, pDC, IL-8, c-reactive protein (CRP) and IFN-g in women with mucopurulent cervicitis (MPC). In women with fertility disorders, chlamydial IFUs correlated positively with plasmacytoid dendritic cells (pDC), IL-10 and estradiol and negatively with CD4 and IFN-γ levels. The data suggest that clinical condition presented is decided by interplay of infectious load and host immune responses.

Significant decrease in levels of IL-8, interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-β) was observed in cervical secretions of Chlamydia positive women with and without infertility after administration of azithromycin as compared to levels before therapy suggesting that azithromycin modulates the production of cytokines in eradication of infection.

In the study on role of iron on pathogenesis of C. trachomatis, expression of transferrin receptor (TfR) was found down-regulated whereas that of ferritin heavy chain (FHC) was up-regulated in C. trachomatis infected HeLa 229 cells. Expression of TfR in infected cells did not change upon addition of iron chelator deferoxamine (DFX) and iron source ferric ammonium citrate. Expression of iron regulatory protein (IRP)-1 predominated over IRP-2 in infected cells. Attenuation in binding activity of iron-responsive proteins and elements was observed in electrophoresis mobility shift assay of infected cells and is central to iron homeostasis.

Leishmaniasis

Identification of a novel ubiquitin-like system in the protozoan parasite L. donovani in infected bone marrow samples from leishmaniasis patients suggested its role in the disease pathogenesis.

Transcriptome profiling for identification of antimony resistance determinants in L. donovani isolated from Indian patients of kala-azar showed genes coding for protein surface antigen 2 (PSA2), histone (H1), histone 2A (H2A), histone 4 (H4) and MAP-kinase. Two hypothetical proteins were transcribed more abundantly in antimony resistant in comparison to sensitive parasites.

In vitro susceptibility of isolates to antileishmanial drugs (miltefosine, amphotericin B, paromomycin and sitamaquine) significantly correlated with one another raising the possibility of cross- resistance. The data indicated paromomycin be more effective treatment option.

Evaluation of host immuno-determinants involved in pathogenesis of kala-azar and PKDL implicated the presence of effector and regulatory molecules together with apoptosis and chemokine related genes.

Analysis of intralesional cytokine gene expression in PKDL and kala-azar revealed significant down-regulation of TNFR1 transcript. Investigation of matrix metalloproteinases provided evidence for role of TIMP-1 and TIMP-3 in pathogenesis of PKDL.

Studies on multilocus microsatellite typing revealed genetic homogeneity of *L. donovani* strains in the Indian subcontinent including Bangladesh, India and Nepal.

STEM CELL BIOLOGY

Pancreatic Progenitor Stem Cells

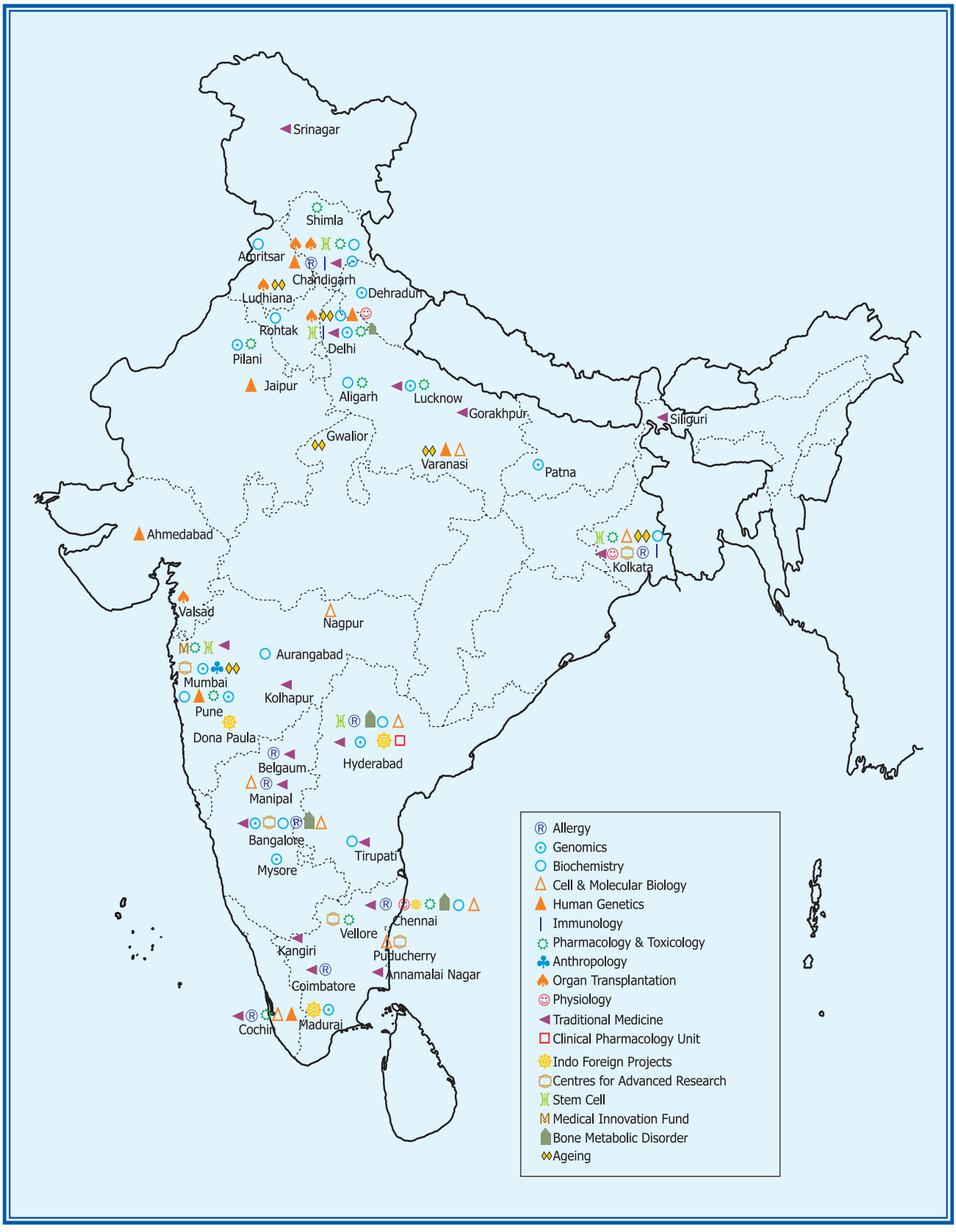
Studies done at NIN, Hyderabad on the role of nutrients in characterization and proliferation of pancreatic progenitor cells/stem cells to insulin secreting cells indicated that nestin, a class VI intermediate filament protein, could be participating in the cytoskeletal formation as well as in cell migration and mitosis.

Studies for Finding Optional Attenuation Conditions for Fibroblasts

Studies were done at IOP, New Delhi for finding optimal attenuation conditions for 3T3 fibroblasts for use as feeder cells. The results indicated that successful attenuation is dependent on numerical dosing with concomitant optimization in the stimulation of keratinocyte cell proliferation. Investigation of the utility of a patented synthetic thermo-reversible hydrogel polymer (TGP) as supportive matrix for development of 3-D composite skin showed that TGP specifically stimulates only those keratinocytes that have inherent stemness.

Derivation of Human Embryonic Stem Cell Lines in Xeno-free Environment

Research efforts at NIRRH are aimed to realize clinical potential of human embryonic stem cells (hES). In order to achieve this, two cell lines have been derived and characterized. To elucidate factors secreted by fibroblasts, differential proteome and genome analysis of feeder fibroblasts, derived from D13.5 (supportive) and D18.5 (non-supportive) mouse embryos was carried out. Correlation of data generated in microarray study with the published proteome data of supportive feeder fibroblasts enabled identification of proteins – which may be the likely candidates in supporting the undifferentiated expansion of ES cells *in vitro.*



Major ICMR Research Projects in Basic Medical Sciences

Results indicate that TGFβ and its associated signaling molecules facilitate undifferentiated proliferation of hES cells *in vitro*.

Cryopreservation and Maturation of Germ Stem Cells for Fertility Conservation of Individuals with Gonadal Insufficiency

Gonadal tissue cryopreservation protocols and culture conditions for *in vitro* maturation of germ cells is being standardized at NIRRH with the aim to preserve fertility of individuals with gonadal insufficiency. The c-kit receptor and its ligand, Sertoli cell factor (SCF), represent one of the key regulators of testicular formation, development and function and have been extensively studied in various animal models. Cellular localization of c-kit receptor (Fig. 5A) has demonstrated, for the first time, a stage specific expression in normal adult human testis. *In situ* hybridization revealed that the transcripts of the gene were also localized in a similar pattern (Fig. 5B). The results will help in expanding current knowledge about the c-kit/SCF system in human spermatogenesis.

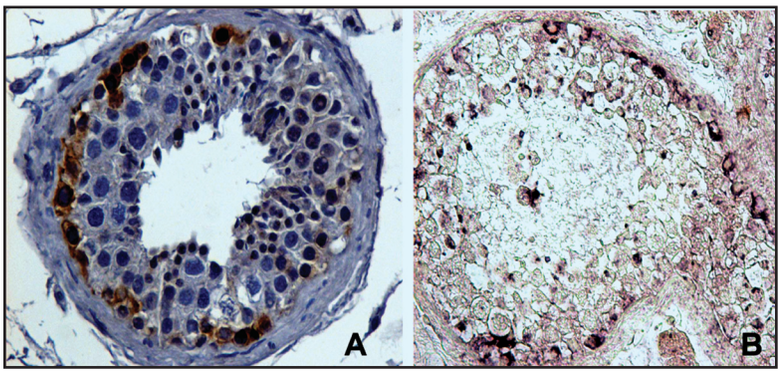


Fig. 5. Immunolocalization of (A) c-kit in the adult human testis. (B) In situ localization of c-kit mRNA.

Stem Cell Therapy

A pilot study was conducted to evaluate the safety and feasibility of autologous olfactory mucosal transplantation in chronic spinal cord injury at Indian Spinal Injury Centre, New Delhi. The results revealed that procedure was tolerated well by all American Spinal Injury Association (ASIA) Impairment Scale (AIS) A participants. MRI evaluation revealed a syrinx in one participant and increase in length of myelomalacia in four participants. There were no other adverse findings on MRI evaluation. There was no significant improvement in any of the neurological, electrophysiological or urodynamic efficacy variables. Statistically significant improvement was seen in functional scores but this could not be attributed to the procedure. Overall the procedure was relatively safe and feasible in participants with thoracic level injuries at 18 month follow up.

BIOCHEMISTRY

A task force study was undertaken on Indian normatives for clinical laboratory parameters (INCLAP). Standard operating procedures (SOPs) and validation of parameters for pilot study has been done so far.

CELLULAR AND MOLECULAR BIOLOGY

A case control study on genetic polymorphism of cholesterol ester transfer protein (CETP) in hyperlipidemic patients at AIIMS, New Delhi demonstrated that genetic factors play a significant role in the predisposition and development of these metabolic abnormalities. CETP TaqIB and apolipoprotein E (Apo E) polymorphism revealed that hyperlipidemic subjects had increased total cholesterol and triglycerides and lower HDL cholesterol. ApoE4 allele was found to be associated with hyperlipidemia.

GENETICS

Neural Tube Defects

Neural tube defects (NTD) are severely disabling central nervous system malformations with worldwide distribution. Certain SNPs in MTHFR gene (C677T, A1298C), have been associated with a variety of multifactorial disorders like neural tube defects, vascular disorders, Down's syndrome, osteoporosis, bad obstetric history and male infertility. Screening of such participants by Council's Genetic Research Centre, Mumbai revealed that 80% were normal (CC) while 20% (CT) showed heterozygosity. No homozygous TT was found in the study group.

GENOMICS AND MOLECULAR MEDICINE

A functional genomics approach to study slow growth phenotype in mycobacteria was undertaken at Indian Institute of Science, Bangalore. Earlier studies in the laboratory had indicated that both *M. tuberculosis*, a slow growing, and *M. smegmatis*, a fast growing mycobacteria, have single copies of functional initiator tRNA gene. To understand the effects of changing the levels of initiator tRNA in the cells, a number of plasmid constructs have been generated for their introduction into *M. smegmatis*. Further studies showed that increase in initiator tRNA levels leads to better fitness. The study showed that antisense against ribosome recycling factor (RRF) mRNA results in growth inhibition.

A study was undertaken at AIIMS, New Delhi to look for changes in CpG methylation at different loci in the genome of tumour cell lines exposed to severe hypoxia. There was a consistent, moderate but significant decrease in CpG methylation at long and short interspersed repeat elements (LINE and SINE) loci. There was also evidence of compromised genomic stability in the hypoxic tumour cell genome. The study of CpG methylation at pro- and anti-proliferative loci gave a mixed result that varied from cell line to cell line and locus to locus.

A fungal protease inhibitor having molecular weight 10.4 kDa was purified to homogeneity from the hemolymph of fifth instar larvae of *Antheraea mylitta* and designated as AmFPI-1. Cloning, characterization and structural biology of this fungal protease inhibitor was done at Indian Institute of Technology, Kharagpur. Data analysis showed that AmFPI-1 contained a single domain possessing a unique fold that consisted of three helices and five beta strands stabilized by a network of six disulfide bonds. AmFPI-1 was found to be expressed mainly in fat body and integument in 4th instar larvae and may help in protection of silkworm from fungal infection.

A study on mechanism and regulation of CD4+ T cell apoptosis by recombinant malaria proteins in mouse splenocytes was conducted at International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi. The results demonstrated that splenic CD4+ T cells from mice immunized with non-replicating immunogens undergo sequential T cell activation followed by activation-induced cell death (AICD). The results provide insight into the mechanism through which two blood stage merozoite antigens trigger different apoptotic programme of AICD in splenic CD4+ T cells.

A multicentric national task force study has developed a protocol for pilot study on newborn screening for the first time in the country at 5 centres (Delhi, Mumbai, Hyderabad, Kolkata and Chennai). In addition, there are centres for high risk screening (Hyderabad and Bangalore), quality control (Hyderabad), data coordination and central Coordination (New Delhi). The study would help understand the disease burden and explore the feasibility of introducing 'universal newborn screening' in India. Study has completed the preparatory phase during which newborn screening has been completed in about 15,000 newborns.

PHARMACOLOGY

A study was undertaken at Indian Institute of Chemical Biology, Kolkata to optimize and evaluate the therapeutic efficacy of galactosylated liposomal flavonoidal antioxidant, quercetin (QC), in combating arsenic-induced hepatic fibrogenesis. Maximal protection from hepatocellular and fatty metamorphosis, necrosis, Kupffer cell hyperplasia, fibrosis and deposition of collagen contents was observed in rats treated with QC before Arsenic injection.

A study on synthesis of monosaccharide derivatives as potential anti-mycobacterial agents was completed at Central Drug Research Institute (CDRI), Lucknow. A different class of compounds was synthesized such as highly substituted enantiopure tetrahydofurans, their pyrazol derivatives, starting form sugars, nitroalkenols, carbasugars, biologically active natural products, substituted enantiopure furans and hex-2-enopyranosid -4-uloses. The hex -2-enopyranosid -4-uloses and their derivatives have shown very promising anti-tubercular activity.

TRADITIONAL MEDICINE

ICMR's Advanced Centre of Reverse Pharmacology in Traditional Medicine established at Medical Research Centre, Kasturba Health Society, Mumbai carried out study of antimalarial activity and clinical safety of traditionally used paste formulation of leaves of *Nyctanthes arbor-tristis.* Trials are ongoing on *Sudarshan Ghanavati* (a multi-ingredient formulation containing *Swertia chirata*) at KEM hospital, Mumbai.

The Centre for Advanced Research in Yoga at Swami Vivekananda Yoga Research Foundation, Bangalore studied neurophysiological correlates of four mental states *i.e.,* Dharna, *dhyana*, *ekagrata* and *chanchalta* or random thinking. All the participants of the study (30) had experience of "Om" and got training for ekagrata one month before participating in the study. The main assessments done were brainstem auditory evoked potentials, (BAEPs), autonomic respiratory variables, functional magnetic resonance imaging (fMRI) and polysomnography. Regarding parts of the brain involved in meditation, midbrain inferior colliculus and bilateral hippocampal activation were found to be involved in *Dhyana* while activation of left hippocampus gyrus was found to have taken place during *Ekagrata and Dharana*. During *dhyana* recruitment of more neurons at the inferior collicular level was found to have taken place. Autonomic and respiratory variables showed reduced psychophysiological arousal, increased skin resistance and decreased breath rate during *Dhyana*. Reduction in slow wave sleep was also noted.

The Centre for Advanced Research in DNA Fingerprinting and Diagnostics of Medicinal Plants from eastern and north-eastern India set up at Bose Institute, Kolkata is engaged in authentic identification of plants for establishing sovereignty rights necessary under the benefit sharing regime, developing precise inventory of medicinal plants in NE India, developing "Passport Data" of medicinal plants for WTO requirement and authentication of vendor supplied plants for production of specific medicines/ pharmaceuticals by the industries. DNA fingerprinting of *Curcuma* and *Zingiber* has been taken up in the first phase. A method for extraction of DNA from rhizomes and leaves of these plants has also been standardized. Polymorphism among 16 varieties of *Curcuma* has been generated using 8 sets of primers.

Under the Golden Triangle Partnership (GTP) scheme on Traditional Medicine, a collaborative project has been initiated between Department of AYUSH, CSIR and ICMR aiming at scientific validation of the traditional systems of medicine. Protocols have been drafted for multicentric clinical trials using integrated approach of modern and traditional medicine for benign prostatic hypertrophy, osteoporosis, hypertension, dyslipidemia and HIV/ AIDS.

Investigation of antimicrobial activity of five traditionally used plant species of Assam was conducted at Assam Medical College and Hospital, Dibrugarh. All the plants showed antibacterial activity against both gram positive and gram negative bacteria whereas antifungal activity was exhibited by three plants. Methanol extract of majority of plants showed antibacterial activity.

Studies were conducted at Indian Institute of Toxicology Research, Lucknow to develop *in vitro* model of ischemic cerebral stroke using PC12 cells. Anti-stroke potential of *W. somnifera* and curcumin was studied in this model. The response was drug specific and curcumin was found to be more effective than W. *somnifera*.

Documentation of Traditional Knowledge about Medicinal Plants of Karnataka

The RMRC, Belgaum has collected information on medicinal plants used for treatment of various diseases by traditional practitioners of Belgaum district. Traditional practitioners were visited personally and interviewed regarding usage of medicinal plants. This study has documented usage of 115 medicinal plants belonging to 56 species to cure 71 types of diseases. The Centre is working in collaboration with local NGOs for documentation and revitalization of local health traditions. Four herbal formulations have been identified for treatment of gastritis and arthritis.

Garden/Museum for Medicinal Plants of Western Ghats

The RMRC, Belgaum has established a garden for medicinal plants of Western Ghats with 79 herbs, 58 shrubs, 33 climbers and 96 species of trees. Each plant is labeled for its scientific, English and vernacular name in various languages with its ethnomedicinal properties.

To create awareness on the importance of the medicinal plants/ethonomedicine and to disseminate scientific information, the RMRC has established a museum of ethonommedicinal plants of Western Ghats. The museum also has a crude drug depository of various parts of medicinal plants in which 280 such samples are displayed.

HAEMATOLOGY

Haematogenetics

Effect of Hydroxyurea in β-thalassemia

Study was done at NIIH in patients of β-thalassemia and HbE-thalassemia treated with hydroxyurea. Results revealed that majority of patients with β-thalassemia intermedia were good responders and improved clinically and were off transfusion within a few months. Hydroxyurea therapy was also helpful in about 60% patients with HbE-thalassemia associated with α-thalassemia and the presence of the Xmn I polymorphs (+/+). The increase in foetal haemoglobin and foetal cells was correlated with increase in mRNA expression.

Identification of Rare Hemoglobin Variants

Some rare α chain haemoglobin variants like Hb Sun Prairie, Hb Jackson, Hb J Paris-I, Hb J-Meerut and Hb O Indonesia were identified using a combination of electrophoretic/HPLC methods and DNA sequencing.

Alpha Haemoglobin Stabilizing Protein (AHSP) as a Genetic Modifier in Clinical Manifestation of β-thalassemia

AHSP is a chain haemoglobin helper which is a chaperone molecule that binds to α globin and prevents the precipitation of excess α chains in β-thalassemia. The sequencing of AL+SF gene has been standardized to look at AHSP haplotypes and mutations in the gene which may ameliorate the clinical severity of β thalassemias. Other genetic modifiers like the ERV9LTR in the HS 5 site of the β globin locus control region (LCR) Ar gene haplotypes are also being studied.

Non-Invasive Prenatal Diagnosis of Haemoglobinopathies

Use of circulating cell free fetal DNA from maternal plasma for non-invasive fetal diagnosis of haemoglobinopathies is being explored. An alternate strategy using a peptide nucleic acid (PNA) with lamp and real time PCR was used for detection of mutation. The paternal mutation could be accurately detected or excluded in few cases tested so far.

Comprehensive Biochemical and Molecular Studies on Unexplained Inherited Haemolytic Anemias

Of the 83 cases of unexplained hemolytic anemias investigated by NIIH, 23 showed RBC membrane abnormalities, two of whom had band 3 protein defects. Five cases had pyruvate kinase deficiency, one had the rare glucose phosphate isomerase deficiency with neurological abnormalities and one case had reduced pyrimdine 51 nucleotidase deficiency. MADH-β5R deficiency was found in 5 cases of methemoglobinemia. Mutations are being characterized in these areas. Two unstable haemoglobins, Hb Sallanches causing Hb H disease and Hb Koln were also identified.

Evaluation of Genetic Factors Related to Unconjugated Hyperbilirubinemia in Neonates

Of the 20 neonates with hyperbilirubinemia screened for the TAn repeat polymorphism and 211(G->A) polymorphism, 9 were heterozygous for 388(G->A) polymorphism and 2 showed homozygous mutant (AA) variants.

Pediatric Immunodeficiency and Leucocyte Biology

Pattern of Primary Immunodeficiency in Western India

A number of facilities were established for the first time at NIIH to evaluate patients with suspected

primary immunodeficiency (PI) disorders. Specialized tests for phagocyte function, hyper IgM syndrome, special lymphocyte subset analysis, X-linked severe combined immunodeficiency and leukocyte adhesion deficiency were standardized for diagnosis of certain immunodeficiency disorders.

Antenatal diagnosis for two couples at risk of leucocyte adhesion deficiency was done on a cordocentesis sample at 18 weeks of gestation for the first time in India.

Genetic Basis of Hemophagocytic Lymphohistiocytosis (HLH)

NIIH has established a number of facilities to evaluate patients with suspected HLH. Of the 16 patients with suspected inherited HLH, 3 showed very low expression of perforin on both NK and CD8 positive T cell populations suggesting severe perforin deficiency. The remaining 3 patients showed partial perforin deficiency in NK cells but normal expression in CD8 positive T cells. Molecular characterization of these cases and standardization of NK cell activity will help in prenatal diagnosis of the condition.

Molecular Characterization of FLT3 Gene Mutation in Acute Non-lymphoblastic Leukemia (ANLL)

Total 276 patients with diagnosed *de novo* acute myeloid leukemia during 2003-2007 were included in this study. Of the total, FLT3 mutation was seen in 24.6%. Amongst the FLT3 positives, 68% had internal tandem duplication, 19% had mutations in tyrosine kinase domain and the remaining 16% showed mutations in other exons of the FLT3 gene. These patients were also screened for JAK2 V617F mutations by allele specific PCR and of the total, 2.3% showed the presence of this mutation. This mutation was seen to be confined to t(8:21) positive AML-M2 and the AML-M4 subtypes, presenting with low peripheral WBC count and low blast percentage as compared to their JAK2 negative counterparts. Also, CD19 and CD56 aberrancy in these cases was found to be significantly higher than in those without the mutation.

Red Cell Serology

Molecular Characterization of ABO Blood Group Antigens in Indian Population

The ABO genotyping was performed on 93 samples from Parsi population by both PCR-RFLP and PCR-SSCP techniques. The A_1O^{IV}, BO_1 and O_1O^{IV} genotypes were found to be most common in this population.

Rh Phenotyping, Detection and Identification of Partial D and Weak D in Rh D Negative Antenatal Women

A total of 250 RhD negative antenatal women were tested for partial D and weak D by ALBAclone Advanced partial RhD typing kit. Eleven partial D individuals were identified (4.4%). Some rare Rh genotypes (rr 19, rr 6 and r^yr1) were identified. The study will be important in selection of monoclonal anti-D reagents used in blood banks.

Identification of Rare Blood Groups in Donor Population

A total of 208 donors were investigated for blood group antigens Kidd, Kell, Duffy, MNSs and Lutheran *etc*. and for Rh genotype. Rare Rh genotypes like Ror, R_1Rz, R_2R_2 of Rh blood group system have been identified. Fy(a+b-) was the most commonly occurring phenotype. The frequency of occurrence of K antigen of the Kell blood group in the donor population was found to be 1.5%. Some donor units negative for common antigens have been identified.

Cytogenetics

Cytogenetic Study of Fanconi Anemia

During 2005-2008 195 aplastic anemia patients, including clinically diagnosed Fanconi anemia (FA) patients were studied. All clinically diagnosed patients exhibited spontaneous and mitomycin C and diepoxybutane induced chromosomal breakage. The major breakthrough of the study was differentiation of FA in 162 aplastic anemia patients without clinical presentation. A significantly high frequency of chromosomal breakage was detected in 12.82% and somatic mosaicism in 4.62% patients

with aplastic anemia. Follow up studies revealed malignancies in 6% patients and clonal chromosomal abnormalities in 55% patients who developed malignancies. The study categorized the patients as clasical FA, somatic mosaic FA, FA without clinical presentation and aplastic anemia.

Telomere and Telomerase Activity in Fanconi Anemia

Study was conducted in patients with Fanconi and aplastic anemia. Telomere analysis was done using quantitative fluorescence *in situ* hybridization (Q-FISH). All the patients showed telomere length reduction and telomere loss. Hence loss of telomere is faster in both Fanconi's anemia and idiopathic aplastic anemia.

Profiling of Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

Study was intiated in 2008 in karyotypically normal MDS and AML patients for their prfiling. The results showed genomic gains and losses in 10 patients at various chromosomal regions such as 1q, 2p,7q, 11q, 17q, 21q, which suggests that other chromosomal locations may be responsible for disease development in karyotypically normal MDS and AML patients.

Cytogenetic Study of Acute Lymphoblastic Leukemia in Young

Out of 172 ALL cases (<15 yrs. old) chromosomal abnormalities were detected in 67%. By FISH technique cytogenetic abnormalities were detected in 83% cases. Some rare translocations like t(12;20), t(2;19) and variant of t(10;14) were also detected.

Thrombosis and Haemostasis

Several novel mutations were detected in hereditary factor VII deficiency, factor X deficiency and in 7% patients with haemophilia B, double mutations were detected. These mutations were analysed by bioinformatic tools to explain how these mutations disrupted the activity of these coagulation factors.

Mutation in von Willebrand Factor Gene in Patients

During the year PCR-RFLP based technique for detecting mutations in some of the exons of von Willebrand factor gene was standardized.

Mutations in Protein C Gene in Thrombophilia Patients with Hereditary Protein C Deficiency

Protein C deficiency is an important cause of hereditary thrombophilia. Of the 2000 patients with venous thrombosis investigated by NIIH, 10% had hereditary protein C deficiency. Of the protein C gene mutations, 2 were novel. One of the mutations, protein C "Sapporo" is a common mutation in Japan and causes abolition of binding in protein C deficient patients.

JAK2-V617F Mutation in Buddchiari Syndrome

Factor V leiden mutation was studied in 80 patients with Budd Chiari syndrome and was found in 15% of them.

Haemoglobinopathies in Tribals

Haemoglobinopathies in Tribals of Orissa

Thalassaemia is considered to be one of the most common monogenic disorders in Orissa. Earlier studies reported the presence of only IVS I-5(G→C) variant in this region,but the current molecular analysis of β gene mutation by RMRC, Bhubaneswar in 431 β thalassaemia cases revealed the presence of IVS I-5(G→C) mutation in 71%, FS 41/42(-TTCT) in12% ,CD 15(G→A) in 7%, CD 30(G→C)in 4.8%, FS 8/9 (+G)in 3% and IVSI-1(G→T) in 2% cases. The tribals possess only IVS I-5(G→C) mutation whereas nontribals possess FS 41/42(-TTCT) , FS 8/9 (+G), IVS I-1(G→T), CD30(G→C) and IVS I-5(G-C) mutations. Clinically anemia was mild to moderate in β thal trait and was found to be associated with majority of abnormalities such as pyrexial episodes, fatigue, headache, lethargy and pallor.

Haemoglobinopathies in Tribals of Madhya Pradesh

The RMRC, Jabalpur continued studies on haemoglobinopathies among the tribals of M.P. Alpha thalassaemia type II was found among *Bharia, Baiga, Kol, Gond* and Pradhan tribes. *Bharia* and *Baiga* are considered primitive tribes. Deletional form of α-thalassaemia was very high in all the six tribes. (Fig. 6). Highest prevalence of alpha thalassaemia (85%) was found in *Baiga* tribe followed by *Bharia* (82%), *Gond*-Patalkot (80.5%),

Gond –Shahdol (75.6%), *Kol* (70%) and *Pradhan* (52%). The gene frequency of (-α) gene was high in *Kol*, *Baiga*, *Pradhan*, *Bharia* , *Gond and Gond* (Shahdol). Such high frequency of α-thalassaemia type II is rarely reported from any indigenous population of the world. $-\alpha^{3.7}$ deletional allele is more common compared to $-\alpha^{4.2}$ deletional allele in all the six tribes.

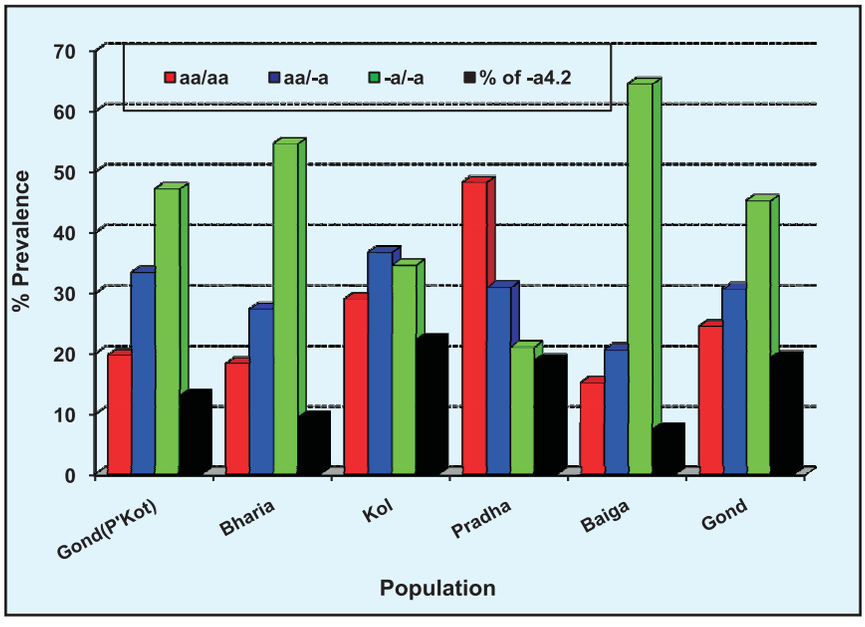


Fig. 6. Prevalence of alpha thalassaemia type II in tribes of Madhya Pradesh

Prevalence of haemoglobinopathies and G-6-PD deficiency varied a lot among the tribes. Sickle haemoglobin was very high (30%) in *Pradhan* of Dindori and moderate (about 15%) in *Baiga* and *Gond* tribes. Prevalence of heat unstable haemoglobin was about 2% in all the tribes except *Pradhan* in which it was 5%.

Studies were also conducted on morbidity profile of sickle cell disease in M.P. For this 243 sickle cell disease (SCD) patients were followed up in an hospital set up. The median age of the hospital based patients was 10.35 yr and there was sharp decline in number of patients >15 yr of age. Bone pain with painful crises, recurrent fever, pallor, icterus and splenomegaly were the common signs in patients. The severity of disease reduced as a result of Centre's intervention in the form of folic acid supplementation and quick treatment along with health education.

Supporting Facilities

The Council's National Institute of Epidemiology (NIE) at Chennai and National Institute of Medical Statistics (NIMS) at New Delhi continued to provide statistical support and consultancy to ICMR and its Institutes/Centres during the year. Both the institutes also extended support in statistical design and computing in clinical trials and carried out epidemiological studies and population research. ICMR School of Public Health at NIE is conducting Master of Public Health (MPH) programme and NIE is continuing its Master of Applied Epidemiology (MAE) programme.

NATIONAL INSTITUTE OF EPIDEMIOLOGY (NIE), CHENNAI

ICMR School of Public Health

Master of Public Health (MPH)

The MPH programme of ICMR School of Public Health commenced from 1st July 2008. Thirteen medical officers deputed by different state governments (Himachal Pradesh, Uttarakhand, Manipur, West Bengal, Karnataka and Kerala) have joined the first batch of MPH programme.

Master of Applied Epidemiology (Field Epidemiology Training Programme) (MAE-] FETP)

During the year 19 scholars were admitted to the course. 16 scholars of the 2006 cohort graduated making a total number of graduates of the programme to 43. In order to involve the MAE-FETP graduates in mentoring, a training workshop was conducted at Kolkata.

WHO/TDR Multicentric Study on Uniform MDT Regimen for All Types of Leprosy

The study enrolled 3396 patients from 2003 to 2008 (India: 3230; China: 166). Of the total, 38% were MB and 4% had grade 2 disability. During follow up, 53 patients developed new lesions. Of these, 47 were on account of reactions. Six patients had clinically confirmed relapse of which three occurred in the first, two during the second and one in the third year of follow up. All these patients were assessed as 'lesion inactive' at the completion of treatment. Subsequently they developed new lesions and were given another course of U-MDT and are being followed up. Clofazimine related skin pigmentation was short-lived and was acceptable to patients. Totally 230 patients were lost to follow up till 2008. Of the total, 2930 completed treatment. Of these, in 16% skin lesions were inactive. PB patients responded better than MB patients. At the end of first, second, and third year of follow up, in 45%, 58% and 77% patients respectively the lesions were inactive.

Disability Status of Post - MDT PB Leprosy Patients in South India

Study was carried out to assess the disability status among 1084 PB leprosy patients >5 years after treatment. It was found that the observed incidence of disabilities was 3.9%, of anaesthesia 2.5% and that of visible deformity 1.4%. Incidence of recovery from anaesthesia was 79% while that of worsening from anaesthesia to visible deformity was 7%.

HIV Sentinel Surveillance in South India

NACO has identified NIE as the Regional Co-ordinating centre for HIV Sentinel Surveillance (HSS) activities in south India. The Institute conducts orientation and training of state surveillance teams (SST), conducts regional review meetings with State AIDS Control Society (SACS), does data entry, identifies testing laboratories and is responsible for quality control and data quality.

Prevalence of Cardiovascular Risk Factors in a Rural Population in Tamil Nadu

Survey was carried out in 11 villages covering 5919 households and population of about 25000. Family history of hypertension, diabetes, heart attack and stroke and prevalence of tobacco and alcohol consumption was recorded. Among males, smoking was prevalent in 47% and chewing in 12%. Alcohol consumption was prevalent among 70% males. Overweight was seen in 27% males and 26% females. Hypertension was present in 22% males and 21% females of which 75% were newly detected during the survey.

NATIONAL INSTITUTE OF MEDICAL STATISTICS (NIMS), NEW DELHI

The NIMS conducted studies on statistical design and computing in clinical trials and epidemiological and population research.

The Institute extended technical support to NACO for HSS and estimated HIV burden in India. Statistical modeling of HIV/AIDS epidemic was also done at NIMS. The Institute monitors clinical trials through Clinical Trials Registry (CTRI) initiated by ICMR. It acted as the national nodal agency for first round of NCD risk factor survey under the Integrated Disease Surveillance Project (IDSP). The survey aimed to estimate the prevalence and distribution of risk factors in various States/regions of India, to establish a database and monitor trends over a period of time. Strategies for interventions will ultimately be evolved to reduce the burden of non-communicable diseases.

A study on evaluation of quality and access to services of adolescent friendly health services in India was taken up at NIMS to evaluate their role, feasibility and sustainability.

Evaluation of Kishori Shakti Yojana (KSY) under ICDS programme of Ministry of Women and Child Development was undertaken in order to apprise its progress and achievements and also to evaluate the impact of various inputs.

Under the Avahan India AIDS Initiative, Integrated Biological and Behavioural Assessment on highways was carried out with the aim to measure the major outcomes and impact of interventions in target populations.

During the year, NIMS was engaged in evaluation of viraemia in healthy volunteers after single dose vaccination with JE live attenuated vaccine. Supervision of data management, statistical analysis and report writing was done.

LIBRARY & INFORMATION SERVICES

As part of modernization of ICMR Libraries, the subscription for the ICMR e-consortia of core journals *Lancet*, *Science*, *BMJ*, *Nature*, and *NEJM* for all ICMR Library and Information Centres has been renewed for one more year as the usage is satisfactory among ICMR institutes. Subscription for full text electronic database ProQuest Health and Medical Complete including ProQuest Medical Library has also been renewed for one more year for seven ICMR institutes. The subscription has been renewed for JCCC@ ICMR (J-Gate Custom Content for Consortia) and J-Gate as the usage of these databases was found satisfactory. ICMR has continued as a member of ERMED Consortia, to develop nationwide electronic information resources in the field of medicine for delivering effective health care. The consortium provides easy access to 1600 medical journals from 9 leading publishers across the world but also makes online journals available to medical scholars working in the country through electronic media. Orientation/ training was organized for scientists on ERMED and ICMR e-consortia and JCCC@ICMR, J-Gate etc. at ICMR Hqrs., New Delhi.

INTERNATIONAL COLLABORATION

The ICMR co-ordinates international collaboration in biomedical research between India and other

countries such as France, Germany, USA, Canada, Australia, *etc*. and with national and international agencies such as Ministry of Science and Technology and WHO *etc.* A total of about 79 exchange visits of scientists to and from India were arranged under various international collaborative projects/ programmes. Progress under MOUs of ICMR with University of Minnesota (USA), CIHR (Canada), University of Sydney (Australia), INSERM (France), BMBF & HGF (Germany), Boston University (USA) to work together on health issues of mutual importance has been made. Joint Working Group meetings of ICMR with University of Minnesota, USA; CHIR (Canada); INSERM, France; University of Sydney/George Institute of Australia as well as S&T Committee meetings of India - Germany, India – Vietnam and India – Spain were held. Indo-German, Indo-French, Indo-Canadian and India – Australia workshops were organized during the year.

During the year three meetings of Health Ministry's Screening Committee (HMSC) were organized wherein approx. 100 projects for international collaboration/assistance with USA, Germany, France, WHO and several other organizations were approved by the Committee.

Under the project "Managing the Indo-German (ICMR-HGF) Science Centre for Infectious Diseases (IGSCID)" four collaborative projects were approved and funded.

ICMR International Fellowships were awarded to five senior and ten young Indian scientists during the year 2008-09.

INTELLECTUAL PROPERTY RIGHTS

A total of five patents were filed with Indian Patent Office during 2008-2009 from intramural research done at VCRC, Puducherry; NIMR and IOP, New Delhi; TRC, Chennai and RMRC, Dibrugarh. One patent was filed by Christian Medical College, Vellore, based on extramural research. One product patent developed by University College of Medical Sciences, New Delhi has been granted. The Council participated in the Indian delegation for negotiation on Global Strategy and Plan of Action Intergovernmental Working Group (IGWG) of WHO. For transfer of technology for commercialization, agreements have been signed between Biotech Consortium India Ltd. (BCIL) and various ICMR institutions. Training programmes were organized in IPR and Technology Transfer for technology managers/ scientists.

TRAINING PROGRAMMES

The ICMR institutes continued to organize training programmes, workshops *etc.* for scientists from India and other developing countries. Consultancy and referral services were also provided to individuals/institutions.

Publication, Information and Communication

A number of activities were continued during the year in the field of publication, information and communication. *The Indian Journal of Medical Research* published by ICMR is available full-text free on the internet. Its impact factor increased to 1.88 compared to last year's 1.67. A number of monographs were also brought out during the year on Indian medicinal plants.

Biomedical Informatics Centre of ICMR is engaged in database and software development, undertaking research projects in bioinformatics and organizing training programmes for the benefit of scientists, students and other medical professionals. Besides this, the Centre also maintains the website of ICMR.

PUBLICATIONS

Indian Journal of Medical Research

The Indian Journal of Medical Research (IJMR) continued to be indexed and abstracted by all major global current awareness and alerting services. The IJMR is available full-text free on the internet (www.icmr.nic.in/ijmr/ijmr.htm) and is also available in the medIND, the online full-text database of Indian biomedical journals.

A special issue on "Metal Toxicity & Health Implications" was brought out in October 2008. Editorials covering themes of various World Days as also on contemporary topics such as HPV vaccine, Global Warming, Heatstroke *etc.* were published. Review articles contributed by eminent scientists from India and abroad on topics of contemporary interest such as Animal Models for Tuberculosis, Malaria in Pregnancy, AIDS Vaccine Trials in India, *etc.* were also published during the period under report.

The impact factor (IF) of the IJMR was 1.88 in 2008 which was highest among Indian scientific journals. Also, the IJMR has crept into the top 50 biomedical journals of the world.

Monographs on Indian Medicinal Plants

The Council is bringing out a series of Reviews on Indian Medicinal Plants. Five volumes of these Reviews have already been published earlier. During the year Vol. 6 and 7 of monographs on about 370 medicinal plants containing multidisciplinary information were compiled and published.

The Council is engaged in development of quality standards of important Indian medicinal plants and preparation of monographs thereon. Quality standards on 49 medicinal plants were developed and Vol. 5 & 6 of these monographs are under print Four volumes were brought out earlier.

Annual Report

The English and Hindi versions of the Annual Report of the Council (2007-2008) were brought out during the year alongwith a compact disc (CD). The reports are also available on the ICMR website.

Hindi Publications

The publication of ICMR *Patrika* was continued during the year. The articles included : *Mrida Sancharit Krimi Sankraman ka Janpadik Rogvigyan aur Niyantran; Bharat mein Asthisushirata ki Sthiti; Orissa ke Vishesh Sandarbh men Aushadh Pratirodhi Falciparum Malaria ki Rogajaanpadiki* and *Sankramak Rogon mein Upasthit Samanya Jivanuon mein Aushadh Pratirodh ki Pahachan Vidhiyan.*

INFORMATICS AND COMMUNICATION

Biomedical Information

The ICMR-NIC Centre's webpage, http://indmed.nic.in continued to be ranked amongst the top Indian health websites by the Google directory.

The medIND database covered 40 journals (approximately 1100 issues). The indexing of journals for IndMED database is an ongoing activity and at present it contains approximately 50,000 records. Updating of the Union Catalogue of Biomedical Periodicals is ongoing with holdings data of 123 libraries updated.

Three training programmes on biomedical information retrieval were conducted during the year at NIC Hqrs., New Delhi (September and December 2008). The training manual was made available from the Centre's website and a hard copy was distributed amongst the participants.

Scientometric Studies

The annual document '2007 Research Output of ICMR Institutes' with analysis of publications from all the institutes including RMRCs was brought out. A total of 444 papers were published by the ICMR institutes during the calendar year 2007. The NIIH, Mumbai topped the tally with 47 papers followed by both NIMR, Delhi and NIN, Hyderabad (41 each). Of the total 67.34% were covered by JCR/ SCI (2007). A total of 258 journals were used for publishing these papers of which 165 were JCR/ SCI covered, 138 with an impact factor (IF) greater than or equal to 1.000. The average IF/paper of the Council was 2.634 for the calendar year 2007. The top five Institutes in terms of total IF were NIIH, Mumbai (92.416), NICED, Kolkata (85.896), NIMR, Delhi (75.842), RMRI, Patna (73.822) and NIN, Hyderabad (70.161).

Bioinformatics Centre

Nine Biomedical Informatics Centres (BIC) of ICMR are working on database development, research in bioinformatics and organizing training programmes in bioinformatics for scientists and medical professionals. Some of the in-house developed databases include database of antimicrobial peptides, integrin-like molecules, biomedical freeware, antimicrobial resistance genes and stress response proteins in microorganisms etc. Some of these databases are available online and have been published or communicated. Research projects have been initiated in collaboration with researchers from host institutes and regional medical institutes in areas such as *in silico* studies on gonadotropins and gonadotropin receptors to identify ligand specificity, creation of electronic patient record system for cervical cytology and endocrinology and homology modeling of acetyl CoA carboxylase from *M. tuberculosis etc*.

During the year, a 23 day training program was conducted at Institute of Bioinformatics and Biotechnology, Bangalore. More than 20 workshops and training programmes have been organized so far.

A comprehensive portal highlighting research activities, databases, web services and publications of Biomedical Informatics Centres has been developed and is available at http://59.160.102.202/bic.

The ICMR website www.icmr.nic.in is updated regularly. An overview of international collaborative projects in biomedical research, development of biomarkers for cardiovascular diseases and diabetes are some of the new features of the website. ICMR *Patrika* (in Hindi) has also been uploaded on the website.

In addition to developing and maintaining software for the purpose of BIC, software development for other Divisions was also undertaken during the year. Extramural Information System for Epidemiology and Communicable Diseases (ECD) Division is helpful in monitoring the extramural research files. When fully implemented, the system will automate major work of the Division.

A software programme has been developed by BIC to facilitate patent analysis for IPR. The programme facilitates searching the text for patent analysis, categorizing in different fields and patent uploading for various diseases.

Another software developed by BIC includes a web based national network of registry for patients hospitalized with acute cardiovascular events. Under the programme data will be collected from patients visiting various hospitals in the country for cardiovascular problems. The software will be applied in 10 major hospitals in March, 2009.

Hindi Day Celebrations

A debate competition on *Bharat mein Chikitsiya Parikshanon mein Nitivishayak Pahaluon ka Anupalan* (Ethical Compliance of Clinical Trials in India) was organized on Hindi Day on September 26, 2008.

ICMR Awards for Medical Books in Hindi

ICMR awards were given for popular medical books in Hindi for the biennium 2006-2007. Dr Rajendra Mehta from Indore bagged the first prize of Rs 50,000/- for his book entitled " *Dama evam Allergy: Kaise Chhutakara Payen".* The book entitled " *Sukhi Balika"* written by Prof Panna Lal of Maulana Azad Medical College, New Delhi was selected for the second prize of Rs 30,000/-. The third prize of Rs 20,000/- was given jointly to Prof Diwakar Dalela and Dr Pratik Sinet of Chhatrapati Shahuji Maharaj Medical University, Lucknow for their book entitled *" Mutra Nali ka Catheter evm Apka Swasthya*".

ICMR Permanent Institutes/Centres

1. National JALMA Institute for Leprosy and Other Mycobacterial Diseases
   P.B.No.1101, Dr.Miyazaki Marg
   Taj Ganj
   Agra 282001

2. National Institute of Occupational Health
   Meghani Nagar
   Ahmedabad 380016

3. National Institute of Epidemiology
   R-127, 3rd Avenue
   Tamil Nadu Housing Board
   Ayapakkam
   Chennai 600077

4. Tuberculosis Research Centre
   Mayor V.R.Ramanathan Road
   (Spurtank Road), Chetput
   Chennai 600031

5. National Institute of Malaria Research
   22, Sham Nath Marg
   Delhi 110054

6. National Institute of Nutrition
   Jamai Osmania
   Hyderabad 500007

7. Food and Drug Toxicology Research Centre
   National Institute of Nutrition,
   Jamai-Osmania
   Hyderabad 500007

8. National Center for Laboratory Animal Science
   National Institute of Nutrition
   Jamai Osmania
   Hyderabad 500007

9. National Institute of Cholera and Enteric Diseases
   P-33, CIT Road Scheme XM
   P.O.Box 177 Beliaghata
   Kolkata 700010

10. Centre for Research in Medical Entomology
    4, Sarojini Street
    Chinna Chokkikulam
    Post Box No. 11
    Madurai 625002

11. Enterovirus Research Centre
    Haffkine Institute Campus
    Acharya Donde Marg
    Parel
    Mumbai 400012

12. Genetic Research Centre
    National Institute for
    Reseach in Reproductive Health
    Jehangir Merwanji Street
    Parel
    Mumbai 400012

13. National Institute for Research in
    Reproductive Health
    Jehangir Merwanji Street
    Parel
    Mumbai 400012

14. Institute of Immunohaematology
    13th Floor, New Multistoryed Building
    K.E.M. Hospital Campus
    Parel
    Mumbai 400012

15. National Institute of Medical Statistics
    ICMR Head Quarters Campus
    Ansari Nagar
    New Delhi 110029

16. Institute of Cytology and Preventive Oncology
    I-7, Sector-39, P.O.Box.No.544
    Near Degree College
    Opposite City Centre
    Noida 201301

17. Institute of Pathology
    Safdarjang Hospital Campus
    Post Box No. 4909
    New Delhi 110029

18. Rajendra Memorial Research
    Institute of Medical Sciences
    Agamkuan
    Patna 800007

19. Vector Control Research Centre
Medical Complex
Indira Nagar
Gorimedu
Puducherry 605006

20. Microbial Containment Complex
Sus Road
Pashan
Pune 411021

21. National AIDS Research Institute
P.B.No.1895 :73, G
Bhosari Industrial Estate
Pune 411026

22. National Institute of Virology
20-A, Dr.Ambedkar Road
P.B. No.11
Pune 411001

1. Regional Medical Research Centre
   Nehru Nagar
   National Highway No. 4
   Belgaum 590010

2. Regional Medical Research Centre
   Nandankanan Road
   P.O. Chandrasekharpur
   Bhubaneswar 751023

3. Regional Medical Research Centre
   N.E.Region, East-Chowkidinghee
   Post Box No. 105
   Dibrugarh 7

ICMR Centres for Advanced Research

1. Centre for Advanced Research in Medical Mycology
   Department of Medical Microbiology
   Postgraduate Institute of Medical Education and Research
   Chandigarh 160012

2. Advanced Research on Liver Diseases
   Department of Gastroenterology
   All India Institute of Medical Sciences
   Ansari Nagar
   New Delhi 110029

3. Advanced Centre for Liver Diseases
   Department of Gastroenterology
   G.B. Pant Hospital
   New Delhi 110002

4. ICMR-NIC Centre for Biomedical Information
   National Informatics Centre
   A-Block, CGO Complex
   Lodhi Road
   New Delhi 110016

5. ICMR Advanced Centre for Research in Nutrition
   Nutrition Foundation of India
   C-13, Qutab Institutional Area
   New Delhi 110016

6. Centre for Advanced Research and Training in Human Molecular Cytogenetics
   ITPL, Whitefield Road, JNCASR Campus
   Jakkur
   Bangalore 500064

7. Centre for Advanced Research in Yoga and Neurophysiology
   Swami Vivekananda Yoga Anusandhana Samsthana
   19, Eknath Bhavan, Gavipuram Circle
   K.G. Nagar
   Bangalore 560019

8. Advanced Centre for Research in Reproductive and
Genetic Toxicology
National Institute for Research in Reproductive Health
Jehangir Merwanji Street
Parel
Mumbai 400012

9. National Tumour Tissue Repository
Department of Pathology
Tata Memorial Hospital
Dr. Ernest Borges Marg
Parel
Mumbai 400012

10. ICMR Centre for Advanced Research in Cancer
Genetics and Genomics
Tata Memorial Hospital
Kharghar
Navi Mumbai 410210

11. ICMR Advanced Centre for Reverse
Pharmacology in Traditional Medicine
Kasturba Health Society
P.O. Sevagram
Wardha
Sevagram 442102

12. Centre for Advanced Research in Pharmacogenomics
Department of Pharmacology
Jawaharlal Institute of Postgraduate Medical Education and Research
Dhanvantri Nagar
Puducherry 605006

13. ICMR Advanced Centre for Research and Training in Evidence
Based Health Care
Department of Psychiatry
Christian Medical College and Hospital
IDA Scudder Road
Vellore

14. Centre for Advanced Research in Stem Cell Research
Department of Surgical Gastroenterology
Government Stanley Medical College and Hospital
Chennai 600001

15. Centre for Evaluation of the Pharmacodynamic Effects of Drugs
Department of Clinical Pharmacology and Therapeutics
The Nizam's Institute of Medical Sciences
Hyderabad 500482

16. National Centre for Culture Collection of Pathogenic Fungi
Department of Medical Microbiology
Postgraduate Institute of Medical Education and Research
Chandigarh 160012