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Editorial

Sexual and Reproductive Health Issues in Women Living with HIV/AIDS, Epilepsy and Gynaecological Cancers

As per WHO, sexual health is a state of complete physical, emotional, mental and social wellbeing in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual and reproductive health requires a positive and respectful approach to sexuality and sexual relationship, as well as the possibility of having a pleasurable and safe sexual experiences, free of coercion, discrimination and violence. Comprehensive sexual and reproductive health programmes and services are the most effective approaches for preventing women mortality, morbidity, fighting HIV and AIDS, preventing and treating gynaecological cancers and meeting the sexual and reproductive health needs of women and young people while promoting human rights.

Healthy women need health care in order to be able to carry their sexual/reproductive function, and to carry them safely and successfully. During the last fifty years, there has been a vast expansion of health technologies and of health services to provide women with certain elements of reproductive health care. These services were not, however, without shortcomings. Apart from inadequate allocation of resources, the major shortcomings were in the philosophy with which services were provided. Women were considered as means in the process of reproduction and as targets in the process of fertility control. The services were not provided to women as ends in themselves. Women were benefitted but were not there at the center of the process. The needs of women have been traditionally addressed within the concept of maternal and child health (MCH). The needs of the women were, however, submerged in the needs of the mother. MCH services tend to focus on the healthy child as the successful outcome. While mother's care is very much needed for this successful outcome because of the investment she make in the process of reproduction, this focus resulted in less emphasis being put on caring for the health risk to which mothers are liable during pregnancy and childbirth, and putting in place the essential obstetric functions and facilities to deal with them. As a result, the tragedy of maternal mortality in developing countries has now reached dimensions that cannot be ignored.

With the mindset that the women are means and not the ends, important health needs in the reproductive process have been left unmet. For example, with all its benefits for the quality of life, the family planning programme has left women with some genuine concerns as well as unmet needs. Contraceptives are meant to be used by women to empower themselves by enhancing their choices, and controlling their fertility, their

sexuality, their health and thus their lives. Family planning, however, can be used and has been used by the governments and others to control birth rather than to empower women. The family planning programme has been largely demographic driven. As far as policy makers are concerned, women were often considered as objects and not subjects. Some governments are short-sighted; not to see that when women are given real choice, and the information and means to implement their choice, they will make the most rational decision themselves, for their communities and ultimately for the world at large.

Infertility may not be a serious hazard as far as physical health is concerned, but can be a major cause of mental and social ill-health. It is not fare that society should provide care to the fertile and reproductive women, but should neglect the suffering of those who are unable to conceive due to infertility or suffering with epilepsy or situations where antiepileptic drug (AED) therapy has made the pregnancy to be a contraindication for such therapy due to a fear of fetal malformation. Sexual intercourse exposes women to the risk of unwanted pregnancy. It exposes many women also to another serious or more serious risk, that of sexually-transmitted infections, including HIV/AIDS. Family planning programmes with an exclusive demographic focus, cannot see the point of this important need for women.

The concept of MCH mainly focuses its attention on women when they are reproducing, to ensure that society gets a healthy child, but often neglects their other reproduction-related health needs. Women's reproduction-related health needs are not limited to reproductive years of their life. The girl child, the adolescent girl, and the mature adult and older woman have health needs related to their future or past reproductive function. Nutrition of women is justified because of the needs of the fetus and the infant who needs a lactating mother. Even with the tragedy of maternal mortality, a justification put forward for investment in keeping mother alive is that their survival is critical for the survival of the children.

The concept of reproductive health has recently emerged in response to the fragmentation of the existing health services and their orientation. The broader concept of sexual and reproductive health offers a comprehensive and integrated approach to the health needs related to the sexuality and reproduction. It puts the women at the centre of the process, as subjects and not objects, as ends and not means. It recognizes respects and responds to the need of the women behind the mother.

It is a matter of great satisfaction that the present issue of Annals contains scientific articles - Surveillance and targeted action to prevent HIV/AIDS, Cancer in Women, Reproductive issues of women with epilepsy and neurocysticercosis as cause of convulsive epilepsy as disease burden in pig farming community, all contributed by very

experienced and learned authors, touch the above issues of women health in one way or the other.

To add as a variety there is an article on a hitherto new approach of the use of deep fascia of the skeletal muscle in cosmetic and plastic surgery. The learned contributor of this paper through a prolonged and sustained investigations has come out with very elegant path breaking research which will benefit reconstructive surgery in many ways.

Dr. Snehalata Deshmukh

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Surveillance and Targeted Action to Prevent HIV/AIDS

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ABSTRACT

Epidemiological surveillance has played a key role in the identification of AIDS and its modes of transmission. In India, laboratory-based surveillance of HIV was initiated among most at-risk populations in 1990s, which was later expanded to antenatal clinics. On the basis of surveillance, high risk geographic areas and high risk populations were identified; and preventive behaviour change interventions were targeted among high risk groups in mid1990s. In 2003, analysis of surveillance data revealed a declining trend in HIV. Further analysis, indicated that targeted sexual behaviour change interventions among high risk groups had been responsible for the decline. The targeted behaviour change strategy among high risk groups was also found to be cost-effective. In the era of anti-retroviral therapy (ART), HIV prevalence trends would no longer be useful for tracking the epidemic. Hence, new laboratory essays are needed for tracking HIV incidence. Verbal autopsy method can provide direct estimates of HIV mortality trends to evaluate the effectiveness of ART. Since the number of new HIV infections is showing plateauing trend, further intensification of HIV/AIDS prevention and control efforts is required to achieve the end of HIV transmission and deaths due to AIDS by 2030.

Keywords: Public health, epidemiology, public health surveillance, HIV/AIDS prevention, control of AIDS, high risk population, sexual behaviour, anti-retroviral therapy.

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Epidemiological surveillance has historically played a key role in not only identification of new diseases but in their prevention, control, and eventually eradication also. The strategy of epidemiological surveillance and containment finally helped in eradication of small pox in the 1970s; and the same strategy is working successfully for eradication of poliomyelitis. Surveillance and targeted action has also played a significant role in controlling HIV epidemic; and now it is possible to plan for achieving zero HIV transmission rate and the end of AIDS by 2030 can be a reality.

Since the early days of 1980s, when Acquired Immunodeficiency Syndrome (AIDS) was recognised among gay men in Los Angeles, epidemiologic methods have not only successfully unravelled modes of its transmission but also paved the way for identification of causative organism – the Human Immunodeficiency Virus (HIV) - leading to the development of rapid diagnostic tests and anti-retroviral treatments.

In India, HIV infection was first identified among female sex workers in 1986. Later, in the same year sex workers started having signs of the disease. By that time there were about 20,000 AIDS cases worldwide, and concerns were raised about the capacity of India in coping with HIV and AIDS. In 1986, Dr. T. K. Ghosh pronounced *"Unlike developed countries, India lacks the scientific laboratories, research facilities, equipment, and medical personnel to deal with an AIDS epidemic. In addition, factors such as cultural taboos against discussion of sexual practices, poor coordination between local health authorities and their communities, widespread poverty and malnutrition, and a lack of capacity to test and store blood would severely hinder the ability of the Government to control AIDS if the disease did become widespread" (1).*

Keeping in view the challenging situation, in 1987, Government established the National AIDS Committee. According to Kakkar *et al.*(2001) by the end of 1987, around 135 people were found to be HIV positive and 14 had AIDS (2). Most of these cases had occurred through heterosexual sex, but by the end of the 1980s a rapid spread of HIV was noticed among injecting drug users in some of the north-eastern states. In order to combat the epidemic, National AIDS Control Organization (NACO) was established and first National AIDS Control Programme (NACP) was initiated in 1992. Its activities covered surveillance, blood screening, and health education. However, doubts were expressed about the extent to which the epidemic had affected Indian population. Dr. L. M. Nath, a leading epidemiologist commented in 1998: *"HIV infection is now common in India; exactly what the prevalence is, is not really known, but it can be stated without any fear of being wrong that infection is widespread... it is spreading rapidly into those segments that society in India does not recognise as being at risk. AIDS is coming out of the closet"(3).*

Therefore, laboratory-based surveillance of HIV, which was initiated in high-risk groups in early 1990s, was expanded to low-risk women in antenatal care clinics in 1998 to monitor the progression of the epidemic in general population. On the basis of limited data available at that time, Rao *et al*.(2001) had predicted a rapidly rising trend in India *"Country level projections ...show adult HIV incidence of 3–4 per cent, which is quite alarming" (4).*

As major rise in HIV had been predicted, we investigated the trend of HIV prevalence in young people attending antenatal care clinics and sexually transmitted disease clinics. HIV surveillance data of women attending antenatal clinics and men attending STD clinics was re-analysed in 2003 in Southern and northern states separately (5). These surveillance data had been collected and analysed by National AIDS Control Organisation every year which had suggested an overall rising trend. However, we noticed that HIV prevalence in women aged 15-24 years in southern states had fallen from 1.7% in 2000 to 1.1% in 2004, but the prevalence did not fall significantly in women aged 25-34 years (6). Therefore, we concluded *"A reduction of more than a third in HIV-1 prevalence in 2000-04 in young women in south India seems realistic, and is not easily attributable to bias or to mortality. This fall is probably due to rising condom use by men and female sex workers in south India, and thus reduced transmission to wives".*

These observations were fiercely contested (7). However, our further analysis of data again in 2004 and 2007 corroborated the declining trend observed first time in Tamil Nadu in 2003 (8). On the basis of surveillance data, high risk geographic areas and key populations had been identified and preventive behaviour change interventions had been targeted more vigorously among high risk groups during the second phase of National AIDS Control Program. The observed decline in HIV was expected.

The targeted intervention (TI) strategy among high risk groups was based on the hypothesis that prevention of HIV transmission from female sex workers to their male clients will result in lower rates of HIV transmission in males and subsequently it will lead to lower rates of HIV in their regular sexual contacts among women in general population. It was expected that this would lead to lower HIV prevalence among the antenatal women, particularly those in the younger age groups, who were more likely to have become sexually active recently. Prevalence of HIV infection in young antenatal women had been considered as a surrogate for the incidence of HIV. In 2003, our analysis of HIV sentinel surveillance data did reveal a declining trend in HIV in India, confirming the hypothesis (5).

Since the contribution of TI strategy in controlling HIV epidemic in program settings had not been formally evaluated, we conducted another analysis of HIV surveillance data to find out whether the trends of HIV decline are associated with

the implementation of targeted intervention programs. We conducted this study in southern states where prevalence of HIV was higher (Tamil Nadu, Karnataka, Andhra Pradesh and Maharashtra). Since targeted interventions had already been implemented, quasi-experimental approach was used to compare changes in HIV prevalence according to the intensity of targeted interventions.

The intensity of TI program implementation was measured by estimating the 'unmet need of condoms', i.e., the number of condoms required minus condoms supplied by TIs. Thus, districts in each southern state were ranked into quartiles based on the intensity of TI implementation. Among female sex workers (FSW), consistent condom use with last paying clients increased from 58.6% in 2001 to 83.7% in 2009. In high TI intensity quartile districts, on an average 186 condoms were distributed through TIs per FSW per year as compared to 45 condoms per FSW per year in the low TI intensity districts. Among young (15-24 years) antenatal clinic attendees, 58% decline was observed in HIV prevalence in high TI intensity districts whereas in low TI intensity districts there was no change in HIV prevalence. This indicated that Targeted Interventions were indeed associated with decline in HIV prevalence (9). We concluded that *"Targeted sexual behaviour change interventions among high risk groups, especially in female sex workers, had been responsible for the observed decline of HIV in India".*

Since large investments were needed to implement a wide range of prevention and treatment interventions, especially due to the need for scaling up of Anti-Retroviral Therapy (ART), the cost-effectiveness of various interventions was also required to refine HIV/AIDS control strategies. Therefore, we evaluated the cost-effectiveness of TI using a mathematical model over a 20-year time horizon, i.e., from 1995 to 2015, with a health system perspective. The incremental costs and effects of targeted interventions for female sex workers (FSW) were compared against the scenario of mass media education for the entire population of India.

Our model estimates indicated that targeted interventions for female sex workers would result in a reduction of 47% in the prevalent HIV cases by 2015. Adult HIV prevalence in India by 2015 would be 0.25% with FSW TIs but with only mass media campaigns the prevalence would be 0.48%. The estimated cost of targeted FSW TI was Rs. 4,748 per HIV infection averted and Rs. 490 per DALY averted (10). We had estimated *"At the current gross domestic product in India, targeted intervention is a cost-effective strategy for HIV prevention in India".*

Hence, HIV preventive programs were continued with vigour despite the resource crunch due to mounting expenditures for scaling up of anti-retroviral therapy (ART). Not only that the number of TIs were increased but the number of surveillance sites were also

increased in 2006, and new HIV epidemics among Men who have Sex with Men (MSM) and Injecting Drug Users (IDUs) were detected, which led to re-characterization of HIV epidemic in India as 'concentrated epidemic'.

As predicted in 2010, according to NACO estimates HIV prevalence among adults of reproductive age has indeed declined to 0.26% in 2015 (11). And now there is a well-established policy that at least 25% of HIV budget should be allocated to HIV prevention despite the need for expansion of the care and treatment programs which are also required to reduce mortality due to AIDS among HIV-infected people.

With widespread availability of ART, it is expected that by 2030 AIDS-related mortality can be totally prevented. Hence, there is need for monitoring cause-specific mortality. But considering the low rates of death registration and cause of death ascertainment in Indian Civil Registration System, it was difficult to monitor HIV/AIDS mortality trends. Hence, we have validated a verbal autopsy method – an interview-based inquiry for identification of probable causes of deaths from the description of symptoms and signs by the relatives of the diseased (12, 13). This field applicable tool proved invaluable in determining causes of death in a representative population. Thus, we could provide direct estimates of HIV-related mortality (about one lakh deaths in 2004) (14). Registrar General of India has incorporated verbal autopsy-based cause of death ascertainment method in the Sample Registration System which will provide HIV mortality trends over time.

Intensification of HIV prevention and treatment is required now more than ever before to stop HIV transmission, end stigma & discrimination, and to end deaths due to AIDS by the year 2030 (15). Newer strategies and resources for expansion of targeted preventive interventions, HIV testing and treatment services are required. HIV testing during pregnancy, as part of prevention of parent-to-child transmission (PPTCT), has expended in recent years, reducing infections in paediatric age-group. This initiative is providing country-wide large dataset for surveillance of HIV infections which is several times bigger than the data collected by HIV Sentinel Surveillance (HSS). However, biases in the PPTCT data need to be evaluated before switching on surveillance from HSS to PPTCT.

Hence, we carried out a systematic appraisal of routinely collected programme data for choosing a scientific, cost-effective, and ethical surveillance strategy. HIV prevalence estimates obtained from PPTCT programme and HSS were compared to find out the utility of PPTCT programme data for HIV surveillance. In 2007, HIV testing rate among pregnant women 76% in 372 ANC clinics where both PPTCT and HSS were carried out. Overall the correlation of HIV prevalence between PPTCT and HSS was 0.9 at state level but it was 0.6 at district or clinic level because the sample size tested at district level in HSS was very small compared to PPTCT (16). We concluded:

"Routinely collected PPTCT program data therefore has potential for providing reliable HIV time trends in various states of India".

These findings again indicating that PPTCT data can provide better estimates of HIV trends for general population even at local ANC clinic or district level. However, since HIV epidemic is now 'concentrated' in the high risk groups, integrated behavioural and biological surveillance (IBBS) assumes more importance. Hence, first IBBS was conducted in 2014 among female sex workers, injecting drug users, men who have sex with men, and transgender people, which provides invaluable insights for refining the program strategy (17).

IBBS has led to discovery of new hotspots among IDUs, MSM and transgender populations in northern India, whereas decline in HIV prevalence has been noted in areas where TI projects had been implemented earlier. However, due to widespread use of ART, HIV prevalence trends no longer would be useful in tracking the epidemic, though prevalence in younger age group (15-19 years) could be used as a surrogate for incident infections.

Incidence of HIV can only be monitored in cohorts, but this is expensive and time consuming. Hence, new laboratory essays are needed which can be used for epidemiological surveillance. We have recently used an avidity essay to indicate recent infections among high risk groups with promising results. Larger studies are required before these can be implemented in the HSS to have an estimate of the HIV incidence trends. In the era of ART, only incidence tracking will indicate at what rate HIV transmission is declining?

HIV surveillance should also employ molecular methods to track emergence of primary drug resistance. Genotyping methods using phylogenetic analysis can also reveal transmission patterns for better targeting of the resource to source population. In view of the current resource constraint scenario, this approach can help in increasing the efficiency of the targeted prevention strategy. Refinement of prevention and treatment strategies and a renewed intensification of HIV/AIDS prevention and control efforts are required now since the financial resource availability has stagnated and the number of new infections are also showing plateauing trend (18).

HIV thrives in key populations which are hard to reach as they face social exclusion due to social stigma and discrimination. Newer approaches are need to improve program coverage beyond 50%. Reaching the last mile with the interventions is much more difficult. It requires addressing other health and social problems faced by these populations such as depression, alcohol use and violence. IBBS should include surveillance for these conditions also, and future interventions would have to address these

problems so that access to prevention and treatment intervention goes up to beyond 90% and high coverage is sustained over long periods of time to achieve the zero HIV transmission and zero AIDS death by 2030 (15).

Only the biomedical approach may not end AIDS epidemic unless we address the social determinants that led to the emergence of HIV and fuelled the epidemic in the last century. A society which creates conditions for large scale unemployment and migration of single young males to industrial areas away from their homes and families, where rampant poverty in the absence of any means of livelihood indirectly promotes the option of selling sex for survival, and where same-sex couples are considered to be criminals, where extreme poverty leads people to forest in search of bush meat, is a fertile soil for emergence and sustenance of not only HIV but also for many other micro-organisms, and societies around the world will continue to pay the price of this social neglect. Emergence of several new infections in last 25 years, i.e., SARS, Ebola, H1N1 etc. are a testimony to this trend. Rapid urbanisation and globalisation would take the newly emerged organisms around the globe in short period of time.

A concerted global response is needed to address the social determinants of health and disease not only for HIV prevention and control but also for prevention and control of many other emerging and re-emerging infections and diseases. The systemic analysis and interpretation of routinely-collected surveillance data will continue to provide newer insights for preventive actions. The targeted public health approach of behaviour change, which led to the decline of HIV in India even before discovery of vaccine or drug for prevention, has once again underscored the importance of public health approach which needs to be nurtured and strengthened in India.

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Cancer in Women

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ABSTRACT

Cancer is emerging as a public health problem among an array of non-communicable diseases. The common cancers in women are breast, cervix uteri, colo-rectum, ovary, corpus uteri, lung and oral cavity. Breast cancer (BC) is the common cancer (20-30% of all cancers in women) and the leading cause of cancer death in women worldwide. About half of the BCs and 60% of the deaths are estimated to occur in economically developing countries. In most of the registries in India, BC is the commonest cancer with the highest incidence of nearly 50 per 100,000 women in Trivandrum. Half of this cancer is reported in <50 years of age and it exercises adverse influence on the productive role of women in the society. The factors that contribute to the international variation in BC incidence rates are largely due to the differences in reproductive and hormonal factors and the availability of early detection services.

Gynecological cancers account 15-30% of all cancers in women. Cervix uteri cancer (CC) is the 3rd most common cancer affecting women worldwide, the most common cancer among women in several less developed countries and 2nd common cancer in India. During last few decades, this cancer incidence has been decreased in India. Significant declines in CC are likely due to changes in marriage and family planning, supported by underlying improvements in education and socioeconomic status. In spite of decreasing incidence of this cancer, gynecologic cancers have increased in India. Among these, ovary and corpus uteri cancers are the major contributors. Ovarian cancer (OC) has emerged as one of the common malignancies affecting women in India and is the 5th common cancer in India (4th common in Trivandrum). A steady increase has been observed in OC incidence in several registries including Trivandrum. More than 50% of women with OC are under the age of 50 years. The risk of it increases in

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women who have ovulated more over their lifetime. This includes those who begin ovulation at a younger age or reach menopause at an older age. Other risk factors include hormone therapy after menopause, fertility medication and obesity. Factors that decrease risk include hormonal birth control, tubal ligation, and breast feeding. Efforts are to be made to detect ovarian cancer at an early stage by educating population about the risk factors. Corpus uteri cancers (CUC) are most common in western countries but are becoming more common in Asia. In India, the highest CUC incidence rates are observed in Trivandrum and its incidence has been increasing. Presently, it is the 5th common cancer among women in Trivandrum, 75% of women are over the age of 50 years. The risk factors of CUC include obesity, diabetes mellitus, BC, use of tamoxifen, never having had a child, late menopause and high levels of estrogen.

Colo-rectal cancer (CRC) is the 2nd most common cancer in women world-wide. The burden of CRC has risen rapidly in some economically developed Asian countries like Japan, South Korea and Singapore. In India, the highest CRC incidence rates are observed in Trivandrum and its incidence has been increasing. Presently, it is the 5th common cancer among women in Trivandrum. The major factors include certain dietary practices and family history of cancer. Individuals with a family history of colon cancer, especially if more than one relative has had the disease, are at increased risk of CRC. Other common cancers in women are tobacco-related cancers such as oral cavity (lip, tongue and mouth) and lung. Declining trends in mouth cancer has been reported in India.

Results on the burden, trends in incidence & mortality, risk factors of breast, cervix uteri, ovary and corpus uteri colo-rectal, lung and oral cavity cancers will be presented.

Keywords : Cancer in women, breast cancer, cervix uteri cancer, corpus uteri cancer, ovarian cancer, colo-rectal cancer, gynecological cancer, hormone therapy, menopause, oral cavity cancer.

INTRODUCTION

Cancer is emerging as a public health problem among women in an array of non-communicable diseases. Among women, it was estimated that 6.7 million new cancer cases and 3.6 million cancer deaths occurred worldwide in 2012 and common cancer sites were breast (26%), colo-rectum (9%), lung (9%), cervix uteri (8%) and corpus uteri (5%) (1). In India, based on the 27 cancer registries functioning under the national cancer registry programme (NCRP) of Government of India, a total of 6,95,693 women cancer cases were estimated for the year 2015 and common cancer sites were breast (27%), cervix uteri (23%), colo-rectum (5%), ovary (5%) and oral cavity (4%). Estimated burden of these

cancers in India were 134,214 female breast; 97,909 cervix uteri; 45,231 ovary; 25, 395 corpus uteri, 30, 309 colo-rectum; 28,542 lung and 39,090 oral cavity for the year 2015 (2). Incidence, mortality, trends and etiology of cancers such as breast, cervix uteri, ovary, corpus uteri, colo-rectum, lung and oral cavity are described briefly.

Breast cancer (BC) is the most common cancer among women in both more developed (MDC) (794,000 cases) and less developed countries (LDC) (883,000 cases, among these 16.4% are from India). Age-standardized incidence rates (ASR) (per 100,000) varied nearly four-fold across the world regions, with rates ranging from 27 in Middle Africa and Eastern Asia to 96 in Western Europe (1). The rate has decreased in the US and many other developed countries since early 2000s (3). However, both incidence and mortality rates have increased in LDCs during the last two decades (4-8). More than 60% of BCs are diagnosed at the local stage in the US (SEER). Conversely, a very high proportion of cases in the developing world are detected in late stages (9, 10). More than 70% of BC patients in high-income countries are diagnosed in stages I and II whereas only 20%-50% patients in low- and middle-income countries are diagnosed in these earlier stages (11).

In India, BC is the commonest cancer in most of the registries with the highest incidence of nearly 50 per 100,000 women in Trivandrum. Time trends in incidence in some areas in India have increased steadily for decades, although the reasons are not well understood (4, 12-14). Pre-menopausal BC comprised substantially a higher proportion of all incident breast cancers in LDCs (average 47.3%) compared to MDCs (average 18.5%). Specifically, 48.4% of BC patients are diagnosed before age 50 years in India while corresponding proportions were 21.5%, 19.1% and 15.9% in Australia, UK and Denmark (15).

Some reproductive factors such as early age at menarche, late age at menopause, decreased total duration of breast feeding, obesity and decreased physical activity have stronger association with the risk of developing post-menopausal BC (16-21). Changes in reproductive and life-style factors mainly affect post-menopausal women whereas genetic factors probably play a more significant role in young women, though these factors alone cannot account for international variation in risk (22). Compared to post-menopausal women, BC in young women tend to display more aggressive features, and as a consequence a higher cause-specific mortality (23-25).

Globally, **gynecological cancers** account for 15-25% of all cancers in women. These cancers rank high in incidence and can affect women of all ages (26). The incidence and mortality rates of gynecologic cancers in Asian countries differ from those in Western countries (1). Cervix uteri cancer remains a major health problem in East Asia, although incidence rates have been decreasing. Behavioral factors such as

delayed and reduced childbearing, use of hormone-replacement therapy and reduced physical activity have also become more prevalent among East Asian women (27).

Cervix uteri cancer **(CC)** is the 3rd most common cancer affecting women with an estimated 528,000 new cases in 2012 worldwide. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. During the past few decades, incidence of this cancer has been decreased world-wide including India (28). Even though the relative importance of this disease has declined, the annual number of cases has increased. There were an estimated 266,000 deaths from CC worldwide in 2012, accounting for 7.5% of all female cancer deaths (1). It is the 2nd common cancer in India with highest ASR in Pazhighat (22.5 per 100,000) followed by Mizoram (20 per 100,000) in North east regions. However in Kerala, low incidence has been reported both in Trivandrum and Kollam (ASR: 7 per 100,000 in both areas) (2). The most important risk factor for CC is infection with the Human Papillomavirus (HPV). Women who smoke or whose mothers were given diethylstilboestrol during pregnancy are also at increased risk for this cancer. The decline in incidence has been attributed to a combination of factors, including improved genital hygiene, changes in marriage and family planning methods, improved treatment modalities and the beneficial effects of population-based cytological screening programmes. Screening via regular gynaecologic examinations and Pap smear followed by treatment of precancerous abnormalities decreased the incidence and mortality of CC (29).

Over the years in spite of decreasing incidence of CC, gynecologic cancers have increased and are contributing about 30% of total cancers among women. Among these, ovary and corpus uteri cancers are the major contributors. The American Cancer Society estimated 88,750 new cases of female genital system cancers in the US in 2012, of which 81,580 cases (78%) belong to the cancers of the corpus uteri (47,130; 53.1%) and ovary (22,280; 25.1%). Estimated deaths for these cancers were 8010 and 15,500 respectively (26).

Ovarian cancer (OC) (239,000 cases and 152,000 deaths) is the 7th common cancer and the 8th cause of death from cancer in women (3.6% of cases and 4.3% deaths). Incidence rates are high in more developed regions, with rates in these areas exceeding 15 and lowest in Sub-Saharan Africa with rates below 5 per 100,000 (1). It has emerged as one of the common malignancies affecting women in India (2). A steady increase has been observed in incidence in several cancer registries including Trivandrum in India (30). More than 50% of women with OC are under the age of 50 years. The risk of it increases in women who have ovulated more over their lifetime. Other risk factors include hormone therapy after menopause, fertility medication and obesity. Factors that decrease risk include

hormonal birth control, tubal ligation and breast feeding (29, 31).

Corpus uteri cancers (CUC) are more common in western countries but are becoming common in Asia. A total of 320,000 new cases (4.8% of cancers in women) and 76,000 deaths (2.1% of cancer deaths in women) were reported world-wide. The highest incidence rates (ASR) were estimated in Northern America (19.1 per 100,000) and Northern and Western Europe (12.9–15.6). Rates are low in South-Central Asia (2.7) and most of Africa (<5 per 100,000). Mortality rates ranged between 0.9 per 100,000 in Northern Africa and 3.8 per 100,000 in Melanesia (1). Increasing incidence rates of this disease have been reported in India (32). Nationally, the highest CUC incidence rates are observed in Trivandrum (6 per 100,000). It is the 5th common cancer among women in Trivandrum (2). Eighty percent of women with CUC are over the age of 50 years. The risk factors for it include obesity, diabetes mellitus, breast cancer, use of tamoxifen, nulliparity, late menopause and high levels of estrogen (29, 33).

Colo-rectal cancer (CRC) is the 2nd most common cancer in women (614,000 cases, 9.2% of the total) world-wide. There is a ten-fold geographical variation in incidence (55% of the cases in more developed regions) across the world, the highest estimated rates per 100,000 were in Australia/New Zealand (ASR: 32.2), and the lowest in Western Africa (ASR: 3.8) (1). The burden of CRC has risen rapidly in some economically developed Asian countries (34) closing the gap to the western, industrialized populations. Economically transitioning countries have reported rapid increases in CRC incidence rates, with rates in the Czech Republic, Slovakia and Japan exceeded those in longstanding economically developed countries such as the United States, Canada, and Australia, these increases are thought to reflect changing dietary and physical activity patterns. In contrast, CRC rates remained stable or slightly increased from registries in majority of developed countries such as those in France, Italy, England, Germany, and Switzerland and decreased in the United States (35, 36).

In India, the highest CRC incidence rates (9 per 100,000) are observed in Trivandrum and its incidence has been increasing. Presently, it is the 5th common cancer among women in Trivandrum (2). The major risk factors include certain dietary practices, reduced physical activity and family history of cancer. Individuals with a family history of colon cancer, especially if more than one relative has had the disease, are at increased risk of CRC. Time trends in incidence in some areas in India have increased steadily for decades, although the reasons are not well understood (37, 38). Given the large population of India, even subtle change in incidence can lead to a substantial burden of disease. CRC can often be prevented through regular screening, which can identify and remove precancerous polyps. The cause of CRC is not known, but age, presence of adenomas in the colon and rectum, family history of

CRC in a first-degree relative, smoking and a diet high in animal fat increase the risk of developing the disease (29).

Lung cancer (LC) is the 3rd common cancer among women world-wide. In women, the incidence rates are generally lower and the geographical pattern is a little different, mainly reflecting different historical exposure to tobacco smoking. Thus the highest estimated age-standardized rates (per 100,000) are in Northern America (33.8) and Northern Europe (23.7) with a relatively high rate in Eastern Asia (19.2) and the lowest rates again in Western and Middle Africa (1.1 and 0.8 respectively) (1).

In India, **LC** was the leading site among tobacco related cancers in 11 registries among women, all the three areas of Mizoram namely, Aizawl District (40.8), Mizoram State (29.3) and Mizoram excluding Aizawl District (21.1) were at the top followed by Papumpare District (16.3) has the highest incidence rate among women (2). Rates of LC in women have been increasing since 1965, with a very modest reduction beginning only in the year 2000 (39). Smoking remains prevalent, especially in younger women (40). Smoking is the predominant cause of LC, and most cancers occur in people who smoke. In addition, non-smoking women are more likely than men to be subject to second-hand smoke from a smoking spouse. Tobacco smoke further increases the chance of developing the disease when other environmental risk factors are present. Other substances that can cause LC, are asbestos, radon, arsenic, chromium, nickel, and tar. However, the impact of these chemicals on the incidence of LC is small compared to smoking (29).

Oral cavity cancer (OCC) accounted for 101,398 new cases in 2012 among women world-wide. The region with the highest incidence was South Central Asia (6 per 100,000) and the lowest rates in Western Asia(1.0 per 100,000) (1). OCC is common in India and is the 5th leading cancer among women. OCC can develop in any part of the oral cavity, the most common sites being the tongue, lip, and floor of the mouth. Rates of OCC are more than two times higher in men than in women. Declining trends in mouth cancer incidence have been in India (2) (NCRP 2016). Studies showed that tobacco use, alcohol consumption, prolonged sun exposure and infection with HPV are the factors increase the risk of developing oral cancer (29).

In conclusion, cancer is emerging as a public health problem among women. Most of the common cancers are showing an increasing trend in incidence except cancer of the cervix uteri and mouth. More than 50% of the cancers in India are reported in <50 years of age and mostly in late stages. Hence it exercises adverse influence on the productive role of women in the society. Public health efforts are to

be made to understand the reasons for the striking increase in incidence of cancers and to promote education and awareness to facilitate diagnosis at earlier stage.

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Reproductive Issues of Women with Epilepsy

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ABSTRACT

There are about 10 million people with epilepsy in India and a quarter of them are women in reproductive age group. The social stigma of epilepsy has pervasive impact on the life of people with epilepsy particularly women. The cyclical hormonal changes during menstrual cycle and during pregnancy can influence the seizure pattern in women with epilepsy. Exposure to antiepileptic drugs (AEDs) can increase the risk of fetal malformations in the infants. This risk is higher with polytherapy and valproate in higher doses. A small proportion of children with antenatal AED exposure can have problems with cognitive development. All women with epilepsy need to have preconception evaluation to simplify the treatment of epilepsy. It is preferable to avoid valproate as an AED antiepileptic drug in women who are planning pregnancy.

Keywords : Epilepsy, pregnancy, antiepileptic drugs, fetal malformation, infertility, cognition.

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INTRODUCTION

Epilepsy is a disease known to humanity from time immemorial. The earliest documentation of epilepsy is in the Babylonian text on Medicine, Sakikku which was written before BC 1000. These stone tablets are saved in the British Museum at London. They have described epilepsy as Miqtu as a collection of what we today label as generalized tonic clonic seizures, absences, drop attacks and focal seizures with or without loss of awareness. They had even described the Jacksonian march of focal motor seizures and seizures characterized by myrthless laughter (gelastic seizures) (1). It was five hundred year later (BC 500) that Hippocrates had broken the myth of supernatural causation of epilepsy. In his text book he has described epilepsy as a disorder of the brain (2). Indian system of medicine had documented epilepsy in detail as early as 6 - 2nd century BC. Indian physicians interpreted epilepsy (apasmara) as a disorder of brain that leads to disturbance in memory or consciousness. Similarly there are detailed description of epilepsy in prehistoric literature from central and south America (3) and Africa (4).

Burden of epilepsy :

Epilepsy is one of the most common serious neurological disorders in the world. It is estimated that there are about 70 million people with epilepsy in the world. There are several studies on prevalence of epilepsy from different parts of India. However there is much variation in the definition, survey methodology, level of ascertainment etc. A meta analysis of several epidemiological studies from different parts of India had shown that the corrected prevalence of active epilepsy per 1000 population was 5.59 with 95% confidence interval ranging from 4.15 to 7.03. Prevalence was higher in rural areas and among men when compared to urban areas and women (5). A recent meta analysis has shown that the median incidence of epilepsy was 50.4 per 100,000 population per year (Inter quartile range was 33.6 - 75.7=6). The incidence in low income countries was higher 81.7 (IQR 28-239.5) when compared to high income countries 45.0 (IQR 30.5 - 66.7). This includes one study from India (6) by Late Prof. K.S. Mani, the father of Indian modern epileptology.

Globally it accounts for 17 million disability adjusted life years (DALY) lost which amounts to 1% of all DALY. More than 90% of these are reported from low and middle income countries. Epilepsy causes a major economic burden to the country. The cost of epilepsy from a nations perspective consists of Direct cost related to Medical expenditures, hospital services, home care services and ancillary services. Another component of direct cost is the cost of the care provided by the family and friends, cost of transportation and housekeeping. The second component of the cost is the Indirect cost related to loss of productivity and earnings by way of absence from gainful employment, income lost by family members etc. A third dimension to the cost

of a disease is the Intangible cost attributed to the pain, suffering and social stigma which is often not taken in to consideration while computing the cost of an illness. We carried out a multi centric study of the cost of epilepsy in India which is the yard stick that WHO often use for the developing world (7). Although the cost of epilepsy in terms of dollars may be low because of the low monetary value of Indian Rupees, it constituted more than 80% of the per capita GNP at that time. More than 70% of the cost of epilepsy was due to indirect component which could be reduced substantially by improving the direct services for diagnosis and treatment of epilepsy. It appears that it is a wise economic decision to invest more on the treatment of epilepsy in order as it is likely to yield considerable savings from lower indirect cost.

Women and epilepsy :

Epilepsy affects men and women in equal proportions. Yet women experience the consequences of epilepsy more than men. The social stigma of epilepsy has more profound effect on women (8). It was observed that the stigma has several levels. On an individual level it leads to lower self esteem, withdrawal, self imposed isolation and a tendency to internalize shame. On a social level it influences social variables such as social integration, social networking and peer group activities. Lastly on a community level it leads to difficulties in arranging marriage or secure a job. In a survey carried out in Kerala state, 31% and 27% thought epilepsy was a hereditary disorder and a form of insanity, respectively. About 40% of the respondents felt that individuals with epilepsy could not be properly educated or employed (9). As a result women have more difficulty in finding a life partner and getting a job. In a direct comparison of men and women matched for age and type of epilepsy it was observed that comorbidities, lower employment and higher anxiety state were more frequent for WWE compared to MWE. Females had more difficulty in finding life partners compared to males. Women with epilepsy (WWE) were at increased risk of divorce (10). The treatment gap is wider for women than for men with epilepsy (11). This gap is even wider when the women live in villages.

Infertility :

On biological terms epilepsy can lead to a variety of medical situations. A survey that compared WWE attending to a tertiary care centre in south India with the women in general in the Kerala state the former had more abortions, smaller family size and greater proportion of women with no living child (12). A subsequent prospective study had confirmed that WWE enrolled in the Kerala Registry of Epilepsy and Pregnancy had higher risk of infertility (38.4%) compared to age matched women in Kerala State (15%). Their family size (0.6) was one third that of women in general (1.87). The risk of infertility increased as the number of AEDs were increased (13). In a follow up study it was also observed that in this registry women with infertility had

abnormal hormonal profile when compared to women who had pregnancy (14). This was characterized by higher testosterone level abnormal LH/FSH ratio and lower progesterone levels in the blood which mimic the anovulatory ovarian cycles and PCOS. In a recent study at our Institute we had observed that 24 % of WWE fulfilled the ATP III criteria for Metabolic Syndrome (15).

Epilepsy and Pregnancy :

Pregnancy can modify the epilepsy in a large proportion of women. Progesterone, the predominant hormone in pregnancy has favourable effects that reduce the seizure frequency as it has antiepileptic properties. In contrast the blood level of several antiepileptic drugs, particularly lamotrigine, oxcarbazepine and levetiracetam are likely to drop considerably in the second and third trimester of pregnancy as their clearance is increased several folds. Data from the KREP indicates that of the 1,297 pregnancies in WWE with complete seizure data, 47.8% were seizure free during pregnancy. Some 15% of women may experience seizure aggravation during pregnancy. Seizure relapse was highest during the three peripartum days. Women with partial seizures or on polytherapy had higher risk of relapse (16).

A variety of complications of pregnancy appear to be increased in WWE such as spontaneous abortion, pregnancy induced hypertension, antepartum or post partum haemorrhage, caesarean section and preterm labour (17). Data from the

Table 1. Comparison of the epilepsy and pregnancy registries

Country	**UK**	**US**	**KREP***	**EUROPE #**	**Australia**
year	1996	1997	1998	1999	2000
Preconception cases	No	No	Yes	No	No
Women not on AEDs	Yes	No	Yes	No	Yes
Exclusion	AED change			AED change	
Data collection	2 contacts	3 contacts	4 contacts	4 contacts	4 (phone)
Outcome ascertained at	<12 wks	< 12 wks	12 months 12 years	12 months	12 months
Control	Internal	External Non epilepsy	External & Internal	Internal	Internal& External

* Kerala Registry of Epilepsy and Pregnancy
# European registry of antiepileptic drugs and pregnancy which also has data coming from south and central America, Japan, Kerala and Australia.

KREP point towards increased risk of spontaneous abortion, gestational hypertension, pre-eclampsia and anemia in WWE when compared to healthy women (18).

The malformation risk of antenatal exposure to antiepileptic drug exposure was first noticed in the 1960s. Since then it had been observed that most AEDs carried increased risk of fetal malformation. Systematic prospective collection of data on the malformation risk for pregnancies in WWE were began with the pregnancy registry in UK in 1996. This was followed by setting up of registry in the North America (1997), Kerala (1998), Europe (1999) and Australia (2000). Most of registries enrol WWE during the first trimester of pregnancy and complete the data collection by 3rd or 12th post partum month. The Kerala Registry of Epilepsy and Pregnancy is unique in enrolling women in the preconception stage or in first trimester and following up their children till the age of 18 years (Table 1).

The overall major malformation rate in the UK registry for all AED exposed cases was 4.2% (95% confidence interval (CI), 3.6% to 5.0%). The rates in the Kerala registry was 7.1% (95% CI 5.98 - 8.44). The risk of MCM with polytherapy is significantly higher than that of monotherapy. Among the monotherapy exposures those exposed to Valproate had significantly higher risk of MCM. Recent studies have shown that the malformation risk increased as the dose of AEDs increased, particularly for valproate, levetiracetam, lamotrigine, cabrbamazepine and phenobarbitone (19). The commonly reported malformations are given in table 2.

Table 2. Commonly encountered malformations in children with antenatal exposure to antiepileptic drugs

Cardiac	
	Atrial septal defect
	Ventricular Septal defect
	Patent Ductus Arteriosus
	Tetrology of Fallot
	Double outlet ventrible
Nervous system	
	Meningo myelocoele
	Spina bifida
	Neural tube defect
	Microcephaly
Skeletal	
	Cleft lip
	Cleft palate
	Tallipes equinovarus
Renal	
	Agenesis of kidney
	Hydronephrosis
	Pelviureteric junction obstruction
	Posterior Urethral valve
	Hyposadias
GIT	
	Omphalocoele
	Cyst in Liver

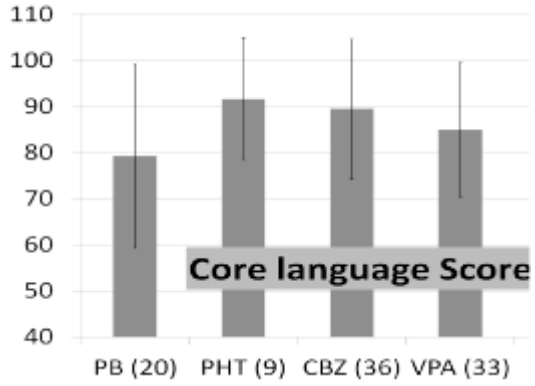

Fig. 1 : Bar chart showing the mean score with standard deviation for the language functions on children with antenatal exposure to different antiepileptic drugs as monotherapy. (PB= Phenobarbitone; PHT=Phenytoin; CBZ= Carbamazepine; VPA= valproate)

The malformation risk of sodium valproate is significantly higher than that of other AEDs according to the data from all the pregnancy registries. As a result it is now recommended not to use valproate as the first drug of choice in newly diagnosed epilepsy in girls and women with childbearing potential.

Cognitive developmental issues of children with antenatal exposure to AEDs :

The negative impact of antenatal exposure to AEDs on the cognitive development of children had been the focus of research in the recent past. The KREP had been prospectively following up a large cohort of such children from birth till adolescence. The setting of the pregnancy registry enabled us to acquire data on the maternal characteristics, AED usage during pregnancy, complications of pregnancy and neonatal status in a prospective manner. Evaluation of these children at one year of age had shown that there is increased risk of motor or mental developmental delay in children with prenatal AED exposure. The risk was higher for those with polytherapy or valproate therapy (20). Further follow up of this cohort at six years showed that they had significantly lower IQ and language performance when compared to school children without antenatal AED exposure (21). This cohort continued to show impairment in IQ, visual reproduction and frontal lobe function when evaluated between 10 - 12 years of age (22). The language functions of children with antenatal exposure to Phenobarbitone was significantly lower than that of children with exposure to carbamazepine or low dose valproate (Fig. 1).

A retrospective analysis of children aged 5 - 9 years with prenatal exposure to levetiracetam, topiramate or valproate monotherapy showed that those exposed to higher doses of valproate had

lower performance on several yardsticks of cognitive function when compared to other AEDs (23). Data from the NEAD study (Neurodevelopmental Effects of Antiepileptic Drugs study) have also confirmed that children with AED exposure, particularly those exposed to high dose valproate had significantly lower IQ when evaluated at one year, three years (24, 25) and six years of age (26). Another retrospective study had shown that those exposed to valproate as mono or polytherapy had higher risk of additional educational needs at school when compared to those exposed to carbamazepine (27). These data have given a clear signal that antenatal exposure to valproate particularly at higher dose can lead to neurodevelopmental problems in children that may persist even to older age. Some of these issues can lead to practical difficulties with education and social adaptation.

Conclusion :

Epilepsy is a common neurological problem in the community. It has considerable ramifications in the biological, developmental, and social domains for the affected person and the family. WWE are exposed to these difficulties to a greater extent than men. WWE in the reproductive age have additional health problems related to pregnancy and structural and cognitive development of their children. Exposure to sodium valproate as an antiepileptic drug in pregnancy can lead to increased risk of fetal malformation and cognitive development. Preconception counselling and optimization of treatment of epilepsy is the key to improve the pregnancy outcome for WWE. It is important to highlight the fact that more than 90 per cent of WWE can expect safe pregnancy and healthy babies. All women need to have a systematic antenatal evaluation and screening for fetal malformation. Children of WWE need to be followed up for possible cognitive developmental impairments so that remedial measures could be instituted as soon as required.

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Neurocysticercosis Burden in Pig Farming Community of North India

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ABSTRACT

Neurocysticercosis (NCC) is the most common cause of acquired active epilepsy (AE). NCC is under reported in India due to lack of systematic systematic studies. We investigated NCC burden in pig farming community of Lucknow district.

Total 294 families with 1640 subjects from 30 villages were surveyed for AE; 595 asymptomatic individuals underwent magnetic resonance imaging of brain. TLR4, MMP9, ICAM1 and GST genes polymorphisms were studied for their role in symptomatic disease. Slaughtered pigs were screened for cysticercosis.

Total 95 (5.8%) subjects with AE were identified; 48.3% of them had NCC. Ninety (15%) asymptomatic individuals had NCC. Thirteen (26%) of 50 pigs slaughtered had cysticercosis.

The results showed high NCC burden in pig farming community and NCC as major cause of AE. Individuals with polymorphic TLR4, MMP9, ICAM1 and GST genotypes were susceptible for symptomatic disease. High swine cysticercosis prevalence suggests the transmission dynamic between human and swine in the community.

Keywords: Active epilepsy, host genetic factors, neurocysticercosis, seizure, swine cysticercosis

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INTRODUCTION

Neurocysticercosis (NCC), caused by the larva (cysticercus) of *Taenia solium* tapeworm is the most common parasitic infection of the central nervous system (CNS). In the developing world, NCC is identified as the most common cause of acquired active epilepsy (AE); 26.3% to 53.8% of AE in the developing countries are due to NCC (1-3). *T.solium* infection is a two host neglected zoonotic disease, transmitted between human and pig, and from human to human. Human is the only definite host, harbouring the adult tapeworm in the small intestine. Pig is the natural intermediate host whereas human is the accidental dead end intermediate host. When human consume cysticercotic pork, the cysticercus develops into an adult worm in the intestine. The terminal gravid segment (proglottid) of the adult worm contains thousands of eggs, which are excreted through faeces contaminating the environment. When eggs are ingested by free roaming swine and accidentally by man through contaminated vegetables, food and water, the eggs lose their coat by the action of the gastric acid and pancreatic enzymes, and the hexacanth embryos or oncospheres are liberated. Oncospheres by using their hooklets cross the intestinal wall and through systemic circulation, they reach the different internal organs of the host, like skeletal muscles, CNS, subcutaneous tissue, eye, etc. Now, the oncospheres lose their hooklets, acquire a vesicular shape and evolve into cysticerci by gradual invagination of the protoscolex (invaginated scolex) in several months (4).

NCC is associated with considerable morbidity related to seizures, strokes, hydrocephalus, and long term treatment; however mortality is minimal and frequently associated only with complicated cases of encephalitis, cerebral edema, hydrocephalus with increased intracranial pressure and stroke. The disease is highly endemic in Latin America, Asia, Africa, and especially in countries where pig husbandry is practiced (5).NCC accounts for approximately 2 million cases with 50,000 deaths per year (6). It is now being increasingly reported in developed countries due to increased travel to disease endemic areas and migration of tapeworm carriers or people infected with the disease from endemic areas (7).

The manifestations of NCC are sometimes polymorphic and some individuals with NCC may remain asymptomatic where parasite dies without treatment, while in others it provokes severe neurological disorders like seizures (8). It has been found that the disease is asymptomatic in the initial phase; however, some patients develop fever and headache during tissue invasion by the larvae but most patients do not become symptomatic until 5 to 7 years after initial infection. Asymptomatic period may range from 1 to 30 years or even more (9, 10). The true incidence of asymptomatic NCC is unknown because studies defining the ratio between the

proportion of the population at risk and those actually has the disease are lacking. Nevertheless, various studies from Mexico and South America have found that up to 50% of patients with evidence of NCC by laboratory testing or neuroimaging are asymptomatic (11). Despite widespread exposure, only few individuals develop symptomatic disease, while others may remain asymptomatic even throughout life but the reasons largely remain unknown. We conducted systematic studies in a rural pig farming community of Mohanlal Ganj block, Lucknow district to estimate NCC burden in symptomatic and asymptomatic individuals, and the possible role of host genetic factors in the development of symptomatic disease. We also examined pigs slaughtered for human consumption for cysticercosis.

Study Subjects:

Total 294 families from 30 villages were chosen based on 30 cluster sampling approach recommended by World Health Organization. Individuals with AE were identified on door-to-door survey. We also examined stool specimens for eggs of *Taenia* to determine the taeniasis burden in the community. Patients with symptomatic disease (AE/ seizure) and asymptomatic (with no neurological symptoms) individuals underwent magnetic resonance imaging (MRI) of the brain. Further, we collected blood from NCC related AE patients (symptomatic) and asymptomatic individuals, and studied TLR4, MMP9, ICAM1 and GST enzyme genes polymorphisms and their expressions to determine their role in the development of symptomatic disease. Pigs slaughtered for human consumption were also examined for cysticercosis by visiting local slaughter houses.

Disease Burden of Taeniasis :

Demographic, clinical and epidemiological data were collected from 1181 subjects in 210 households in 30 villages. Stool specimens from 924 subjects were examined for eggs of *Taenia* and other parasites. Eggs and/ or proglottids of *Taenia* species were detected in 172 (18.6%) individuals. This is one of the highest rates of taeniasis reported in literature. Factors associated with intestinal taeniasis on multivariate analysis were age above 15 years, history of passage of *Taenia* segments in stool, undercooked pork consumption and poor hand hygiene (12). In an earlier study from Uttar Pradesh, overall prevalence of T. *solium* taeanisis was 2% in the community (13). In Chandigarh (India), the prevalence of taeniasis ranged from 0.5-2% in hospitalized patients and 12-15% in labour colonies where pigs were raised (14). In Goa, the estimated prevalence of taeniasis was reported to be 9.7% (15).

Prevalence of Symptomatic/ Asymptomatic NCC :

Total 95 of 1640 (5.8%) subjects surveyed in the community had AE; 48.3% of them had NCC on MRI. Single cyst (cysticercus) was detected in 21 (47.7%), two cysts in 11 (25.0%) and

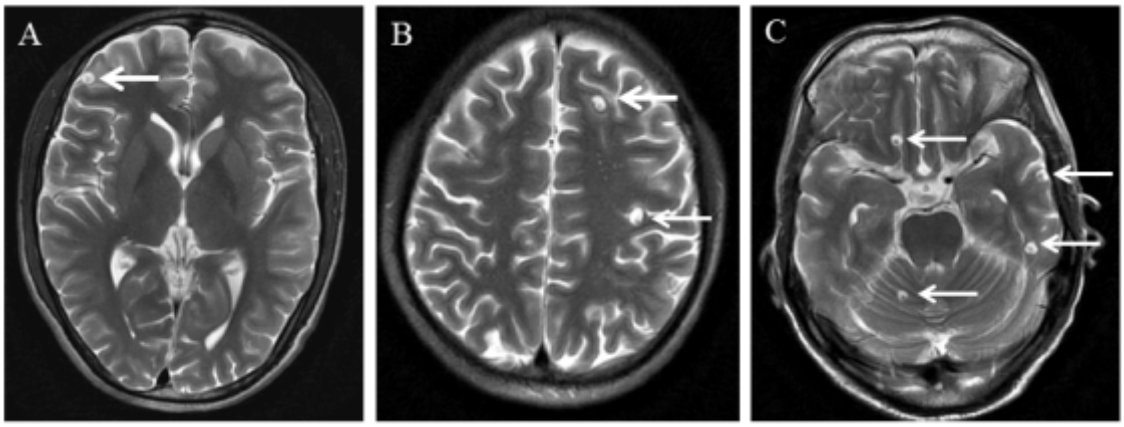

Fig.1 : Magnetic resonance image of symptomatic patients with neurocysticercosis showing cysticerci in the brain parenchyma.T2-weighted axial images at different sections show(A)single cyst, (B)two and (C)multiple cysts.

multiple cysts (>2) in 12 (27.3%) patients. MRI pictures of individuals with single cyst, two and multiple cysts infections are shown in figure 1. Occurrences of vesicular (viable), colloidal/degenerating, calcified and multiple stages of cystic lesions were detected in 2 (4.5%), 9 (20.5%), 21 (47.7%) and 12 (27.27%) individuals respectively. The cystic lesions were present in the parenchyma in all the patients; however, two patients with multiple cysts showed a parasite lodged in the subarachnoid space along with parenchyma(16). Epilepsy in the family and no separate place for pig rearing were identified as risks for NCC clustering. The treatment gap for AE in the community was above 90%. The probable reasons for such a high treatment gap were economic, lack of medical facilities, social prejudice and faith in other alternative treatment modalities. The prevalence of NCC related AE and epilepsy as such in the pig farming community was tremendously high. In the developed world, the prevalence of AE varies from 3 to 9 per 1000 populations as compared 49 per 1000 populations in Liberia (17, 18). In our study the prevalence of AE was strikingly high (5.8% i.e. 58 per 1000 populations) and 48.3% of them had NCC. In South India, the prevalence of NCC related AE varied from 28.4% to 31% (19, 20).

Total 90 of 595 (15%) asymptomatic individuals who underwent MRI had NCC. Single cyst was found in 65(72.2%) followed by two cysts in 16 (17.8%) and multiple cysts in 9 (10.0%) individuals. MRI pictures of asymptomatic individuals with single cyst, two and multiple cysts infections are shown in figure 2. Occurrence of vesicular, degenerating, calcified/healed and multiple stages of cystic lesions were detected in 16 (17.8%), five (5.6%), 58 (64.4%) and 11 (12.2%) individuals

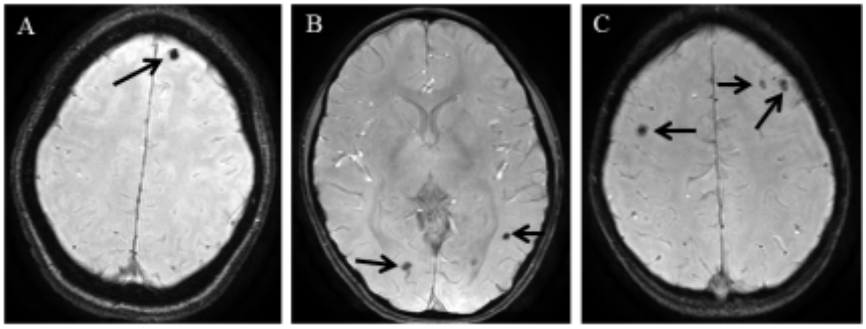

Fig.2 : Magnetic resonance image of asymptomatic neurocysticercosis subjects showing cysticerci in the brain parenchyma. SWAN images at different sections show(A)single cyst, (B)two and (C)multiple cysts.

respectively. The distribution of multiple stages as follows: vesicular and degenerating in two, vesicular and calcified in six, and degenerating and calcified in three cases. Most of the cystic lesions were present in the frontal lobe of the brain (51.1%), followed by multiple locations (14.4%), occipital (13.3%), parietal (11.1%) and temporal (6.7%) lobes. All the cysts were located in the parenchyma of the brain except one cyst each in ventricle, thalamus and choroids plexus of the brain (21). Comparative distributions of cyst burden according to number, location and stage of the parasite in symptomatic and asymptomatic NCC cases are given in figure 3. A study from Mexico showed that 9.1% of apparently healthy subjects had calcified NCC lesion, mostly located in the frontal lobe on CT and these individuals were totally symptom free (22).

The number, location and stage wise cyst distributions in symptomatic and asymptomatic subjects were

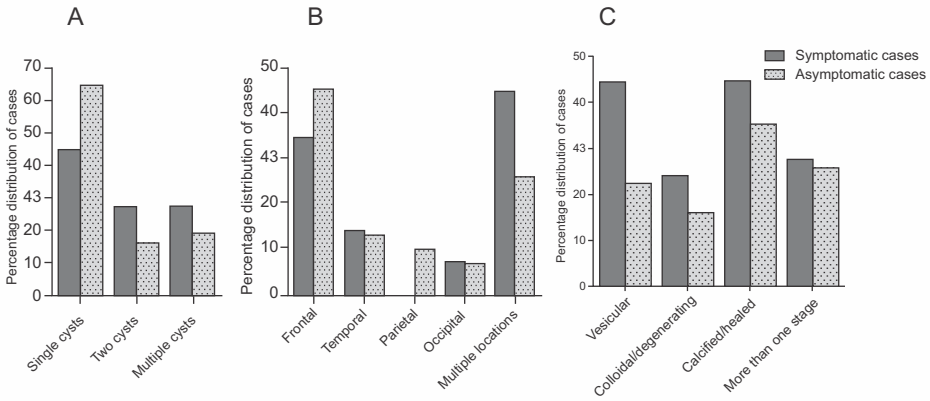

Fig. 3 : Distribution of cysticerci burden in symptomatic vs. asymptomatic NCC cases according to (a) number, (b) location and (c) stage.

comparable (Figure 3). Now the question arises why some individuals develop symptomatic disease (seizure), while others with similar number, location and stage of the cysticerci remain asymptomatic. Do host genetic factors have some role in the development of symptomatic disease? To answer the above question, we planned to study various host genetic factors and their association with symptomatic disease.

Host Genetic Factors and Symptomatic NCC :

Most of the human disorders are results of interactions between environmental and genetic factors. Helminths expressed glycans (glycoproteins and glycolipids) may activate host immune cells and some of these molecules can act as specific pathogen associated molecular patterns (PAMPs) for particular TLRs (23). Thomas *et al* (2003) showed that helminthglycans could act as PAMPs for inducing potent Th2 response via TLR4 dependent mechanism(24). Since studies are lacking, we investigated the role of TLR4Asp299Gly and Thr399Ile polymorphisms and their role in the development of symptomatic NCC.

Our results showed that TLR4 Asp299Gly and Thr399Ile were significantly associated with the occurrence of NCC and progression to symptomatic disease compared to healthy control and asymptomatic NCC subjects. Haplotype Gly/Thr was observed as a risk factor for susceptibility to NCC. Gly and Ile carriers had significant association with symptomatic NCC (25).

Our earlier studies showed significantly enhanced expressions of MMP-9 and ICAM-1 in symptomatic NCC patients (26, 27). We further evaluated the MMP-9 and ICAM-1 gene polymorphisms in NCC subjects. The analysis of the genotype frequency of MMP-9 (R279Q) polymorphism revealed a significant association of the heterozygous genotype (R/Q) with symptomatic subjects compared to asymptomatic subjects. However, there was no significant difference in the genotype frequency between asymptomatic NCC subjects and controls (28). In ICAM-1 K469E polymorphism study, homozygous (EE) variant genotype was associated with 11 and 4 folds increased risk of symptomatic disease when compared with healthy controls and asymptomatic NCC subjects respectively. However no such association was found between healthy controls and asymptomatic NCC subjects. Further, the E allele had significant association with symptomatic NCC than controls and asymptomatic NCC subjects. The K allele was more prevalent among the healthy controls and showed protective association when compared with symptomatic NCC subjects (29).

Previously we reported higher expression of pro-inflammatory cytokines in symptomatic NCC patients (30). Inflammatory cells with production of inflammatory cytokines activate cellular oxidant-generating pathways. Reactive

oxygen species (ROS) that are generated during inflammatory conditions are highly reactive and can cause damage to cellular macromolecules such as lipids, DNA and proteins (31). To counteract the damage from ROS, the cells are endowed with a glutathione antioxidant system, which includes glutathione reductase, glutathione peroxidase, and glutathione S-transferases (GSTs).These enzymes maintain redox balance and protect cells from oxidative damage (32). In humans, the GST enzymes can be divided into five main classes: alpha (GSTA), mu (GSTM), pi (GSTP), theta (GSTT), and zeta (GSTZ) that are critical in protection of cells from ROS during inflammatory condition (33-35). These GSTs are polymorphic in nature with reported inter-individual variations in their enzymatic activity and level. However, the role of GSTs in NCC remains unexplored. We investigated the polymorphisms in GST genes and their expressions and activities in symptomatic and asymptomatic NCC subjects.

Human GST gene polymorphisms study revealed that the individuals carrying the deletions of GSTM1 and GSTT1 (null genotypes) were at risk for developing symptomatic NCC disease. Genetic variants of GSTM3 and GSTP1 were not associated with symptomatic disease. The total GST activity and levels of GSTM1, GSTT1, and GSTM3 were significantly higher in asymptomatic subjects than in symptomatic and healthy controls. Lower GST activity was observed in individuals with GSTM1 and GSTT1 deletions. The study suggests that the individuals with GSTM1 and GSTT1 deletions are at higher risk to develop symptomatic disease because such individuals have low level of GSTs that fail to protect tissues from ROS related oxidative damage. The higher GST activity and levels of GSTM1, GSTT1, and GSTM3 are likely to protect tissue from oxidative damage thus maintaining asymptomatic condition (36).

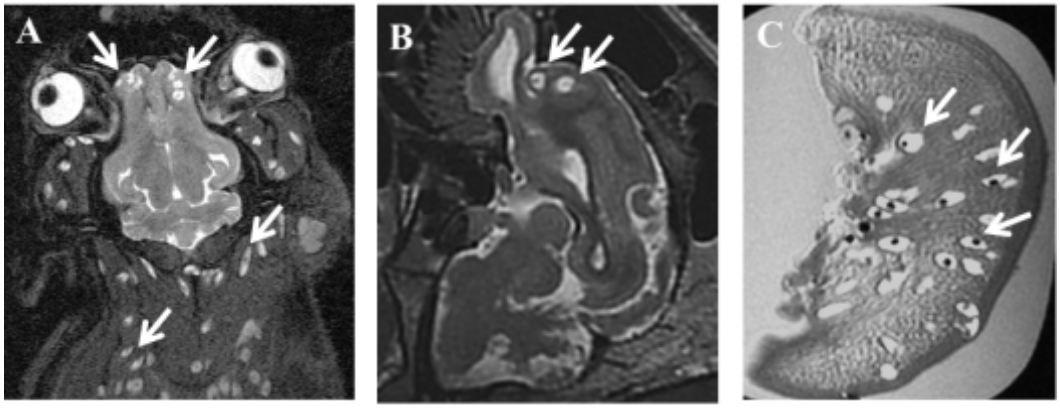

Fig. 4 :T2-weighted magnetic resonance images of pig brain(A and B), and tongue (C) showing large number of cysticerci (arrowheads).

Prevalence of Swine NCC :

Our slaughter housesurvey showed that 13 (26%) of 50 pigs slaughtered for human consumption had cysticerci in their muscles; 5 (38%) and 3 (23%) of them also had cysticerci in the brain and liver respectively (37).Further, we developed MRI protocol to detect neurocysticercosis in swine for the first time (38). We also identified several clinical signs of swine NCC and these signs (excessive salivation, excessive blinking and tearing, and subconjunctival nodule) were reported for the first time in literature(39). Other Indian studies showed that 8-10% of pigs slaughtered for human consumption in Chandigarh and 7% in Kolkata had muscle cysticercosis (14,40). MRI of pig brain and tounge with cysticerci are shown in figure 4.

Conclusion :

The study shows high prevalence of taeniasis and NCC related AE in the pig farming community of North India with tremendous treatment gap. Individuals with polymorphic genotypes of TLR4, MMP9, ICAM1 and GST are more susceptible to develop symptomatic disease (seizure episodes). High human taeniasis and swine cysticercosis prevalence suggests the dynamic of transmission cycle in the community between human and pig. Since cysticercosis is a preventable disease, appropriate measures like health education, improved sanitation, mass awareness, better medical facilities, mass treatment of *Taenia* carriers, and restriction on sale of measly pork may help to reduce the disease burden and economic loss to the country.

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Experimental and Clinical Evidence Based Rationality of Incorporation of Deep Fascia in Tissue Transfer for Reconstructive Surgery

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ABSTRACT

Intense clinical research since 1984 through 93 parameters has unveiled the rationality of reconstructive procedures with several new concepts and innovative techniques of various compositions. Such extensive work has been done totally in our country popularizing the techniques amongst the plastic surgeons of the world. This presentation deals with the tissue constituents and vascular network of the deep fascia. This sustained research was conducted at inter-departmental, interfaculty and interinstitutional levels.

Fresh cadaveric dissections, animal experimentations and clinical research revealed crucial findings applicable for resurfacing defects of different etiology and magnitude. The deep fascia covering the muscle is thought be an inert a avascular structure with protective function only. We have demonstrated for the first time in the world the live vascular and lymphatic microcirculation in deep fascia proving it to be having dense vascular network. Therefore its incorporation during the reconstructive surgery enhances the vascularity allowing transfer of large dimension of tissue for reconstruction in cases of trauma, infection, cancer surgery, etc. It has proved the rationality of these procedures convincingly to the scientific world.

Histology of deep fascia showed rich subfascial and suprafascial arterioles and capillaries. Intrafascial course of the perforating vessels from the subfascial plane to the suprafascial plane was visualized. Confocal microscopic analysis of fluorecenised deep fascia under 40X magnification showed longitudinally aligned collagen fibres and nuclei of multiple fibroblasts. Electron microscopic Y of deep fascia revealed (a) Elastic tissue and collagen fibres, (b) Lymphatic vessel, (c) Thin walled venule with

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COL. SANGHAM LAL MEMORIAL ORATION delivered during NAMSCON 2016 at the All India Institute of Medical Sciences, Raipur.

single layer of muscle fiber, endothelial cell nucleus, Venules with multiple RBCs, mast cell with granules and capillary showing endothelium and endothelial cells.

Angiography in experimental model and patients, demonstrated longitudinally oriented vascular network in deep fascia and fasciocutaneous flap. Live microcirculation and Lymphatic circulation in the human deep fascia was demonstrated first time in the world under 150 and 600 magnifications.

Keywords : Deep Fascia, reconstructive Surgery, Microcirculation.

INTRODUCTION

Frequently resurfacing of defects is required following trauma, excision of malignant lesion, avulsion injuries, chronic wounds, etc. Lower limb is often involved. The composite soft tissue commonly used for reconstruction consists of skin, subcutaneous tissue, deep fascia and/or muscle (1). The vascular supply exists in all these tissue planes in the form of dense vascular arcade. In the lower limb, there are three main vascular trunks namely, posterior tibial, peroneal and anterior tibial. Small vessels arise from them which perforate different tissue planes and are called 'perforators'. There are musculocutaneous, septocutaneous and direct cutaneous perforators (2). As they pass through different planes, dense vascular networks are formed which communicate with each other (3). Thus a continuous flow of blood is ensured in the composite tissue transfer by incorporating the perforators and the vascular network of tissues (4). In this context the deep fascia covering the muscles plays an important role. It is a highly vascular structure contrary to the common belief. It has a suprafascial and a subfascial vascular plexuses.

Therefore to ensure circulation, knowledge of two aspects is important.

(1) Main vascular trunks and perforators.
(2) Vascular network in the tissues.

Why it is necessary? It explains in clinical practice how large dimensions of tissue are successfully transferred based on only these perforators and the vascular arcades (5). Hence to understand the *dynamics of circulation*, we need to know about supplying vessels and the microcirculation in the tissues. *Knowledge of perforators deals with location, number, caliber, direction, and the perfusion pressure. Microcirculation includes two systems, vascular and lymphatic*. To convince the scientific world, evidence based proof is necessary regarding the above features. This presentation distinctly emphasizes the rationality of the success of these reconstructive procedures. There are different methods to visualize the perforators. They are :

(a) Histology of deep fascia
(b) Old and fresh cadaveric dissections
(c) Audio Doppler
(d) Color Doppler

(e) CT angiography with 3D reconstruction. All these findings establishing the practical utility in reconstructive surgery has been conducted in our institute through collaboration of different departments. Such research requires original thinking and formulation of experimental and clinical model.

Histology of deep fascia and cadaveric dissection :

The knowledge regarding the structural details of deep fascia remains inadequate. It was described to be relatively avascular covering the muscles having predominantly protective function. Some studies revealed that it has associated vascular arcade and hence its incorporation ascertained additional vascularity to the flaps. *Light microscopy (10X & 40X)* of fresh human deep fascia harvested from the covering of the gastrocnemeus muscle was done. It showed arteriols and capillaries in both the layers of deep fascia (suprafascial and subfascial plexes). They could be seen traversing the intrafascial course. Under *electron microscopy (4000X)*, arteries, capillaries, venules and lymphatics could be seen apart from other structural elements (6) (Figs. 1a, b, c, d). They all contribute to enhance the vascularity and

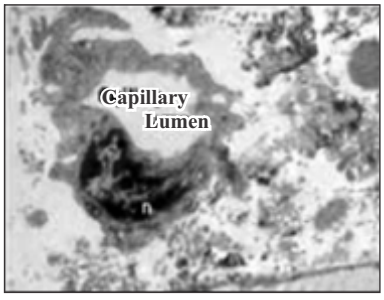

Fig. 1(a)

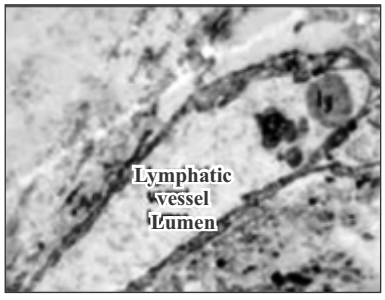

Fig. 1(b)

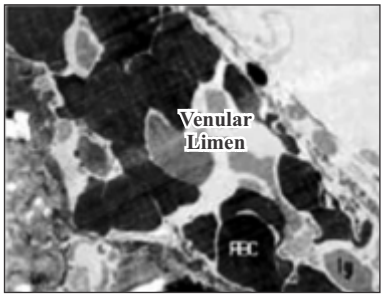

Fig. 1(c)

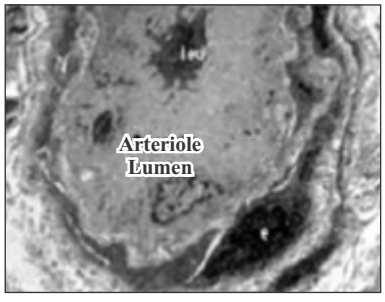

Fig. 1(d)

Fig. 1 : Electron microphotograph of the deep fascia showing (A) Capillary, the single endothelial cell nucleus (n) (x4000). (B) Lymphatic vessel with lymphocyte in the lumen (ly) (x4000). (C) Venule with lymphocyte (ly) and RBCs in the lumen (x 4000). (D) Arteriole with leukocyte (leu) in the lumen (x4000).

maintain the physiological functions of the transferred tissue.

Dissection on old cadavers in the lower limb revealed *presence of perforators of different sizes, arising from the main vascular trunks, at regular intervals.* Similar findings were confirmed in fresh cadaveric dissection after injecting dye in the poplitial artery (7) (Figs. 2 & 3). During operative procedure

Fig. 2 : Cadaveric dissection showing distal posterior tibial perforators.

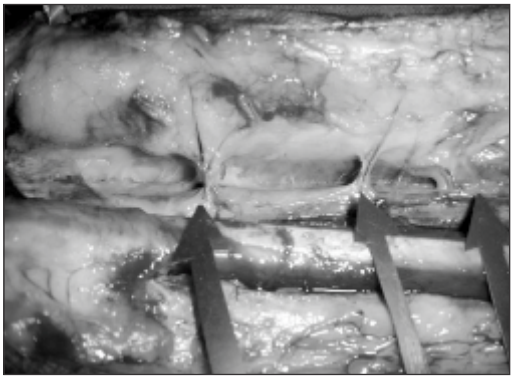

Fig. 3 : Fresh cadaveric dissection showing perforators with their vena comitantes, either branching prior to reaching the fascia or continuing without branching.

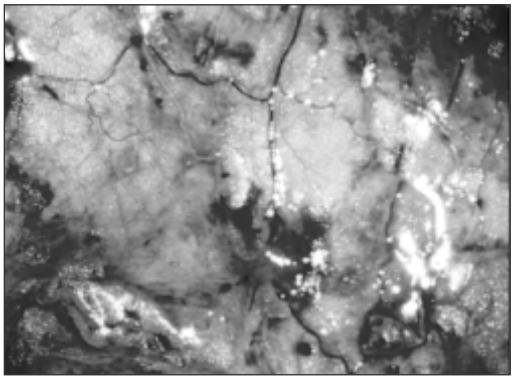

Fig. 4 : Intraoperative view under magnification showing the intrafascial course of the perforator merging with the subfascial plexus.

of flap elevation, exploratory incision also confirms the location of these perforators. Intraoperatively under magnification the intrafascial course of the perforator merging with the subfascial plexus can be witnessed (Fig. 4).

Doppler studies :

Color Doppler provides important information regarding the location, direction, length and the internal diameter of the perforators. In clinical practice, the Audio Doppler can locate them and provides idea about their dimension depending upon the intensity of sound.

CT Angiography :

The evolution of flaps has come a long way in terms of tissue constituents and mode of transfer. This advancement could be possible due to better delineation and understanding of the vascular system and its ability to perfuse a flap (8). The locoregional perforator flaps are preferred

for reconstruction whenever adjacent normal tissue of required dimension is available. The two most important reasons are that :

(a) It does not sacrifice any major vessel in an already traumatized limb and

(b) It does not require microvascular free tissue transfer. However, a free flap from a distant area can also be planned to be anastomosed to a perforator. Thus the knowledge of perforators is of significant value whether one chooses to apply a locoregional flap or a free flap depending upon the situation. The perforator flaps evolved on the knowledge of the vascular tree from the main vascular trunk up to the subdermal plexus. Therefore, we thought that it was necessary to map the whole vascular arcade in the lower limb.

To evaluate the perforators and the whole vascular tree, peripheral CT angiography with 3D reconstruction was done. It helps in designing flaps of different constituents based on the selected perforators. CT angiography was done using a non-ionic iodinated contrast media injected through the antecubital vein. The lower limbs were imaged using volume rendering CT scan machine. Three dimensional reconstructions were made. The whole arterial tree, along with the perforators, was mapped. The three dimensional CT angiographic reconstruction with bone and soft tissue provided advanced knowledge of this vascular network (9) (Figs. 5 & 6). It delineated the main vessels, the perforators, their caliber, inter -perforator

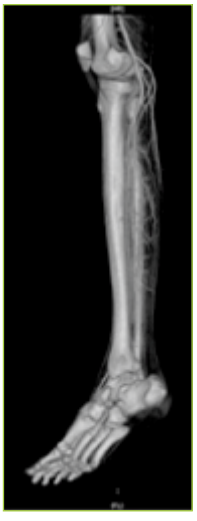

Fig. 5 : CT angiography showing the perforators of the posterior tibial artery.

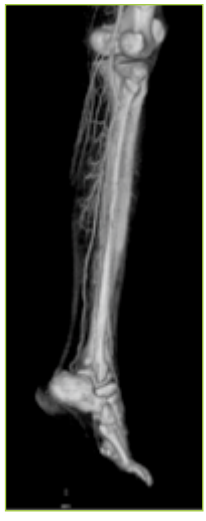

Fig. 6 : CT angiography showing the perforators of the peroneal artery.

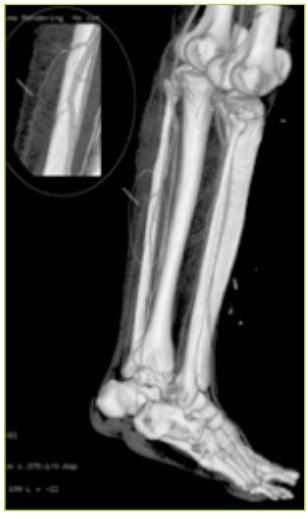

Fig. 7 : (a) Course of the perforators up to the subdermal plexus of the posterior and peroneal arteries (b) The inset showing the magnified view of the course of the peroneal perforator.

distance, direction, distance from fixed bony landmarks and course up to the subdermal plexus (Fig.7).

By 360 degree rotation and dynamic 3D CT reconstruction, every detail of the vascular tree could be delineated which otherwise will be missing in a single slice. This is an advancement over the existing two dimensional sagittal tomography which does not provide the detailed findings required for reconstruction. The intra-operative findings of perforators during flap dissection confirmed the accuracy of peripheral CT angiography.

Perfusion pressure :

We correlated between the internal diameters of perforators with their perfusion pressure. This is an important step towards understanding how much tissue is supplied by a perforator. It is difficult to assess the angiosome of the perforators. However it is well established now that due to the rich inherent vascular network of the deep fascia, one can dissect a large flap of nonconventional dimension (beyond 1:2) safely and it behaves like an axial flap. This is because the vascular networks of adjacent perforators freely anastomose with each other and make an effective continuous vascular channel. The standardization was done in the experimental model in rats in the department of physiology. Prior to measurement, color Doppler gave the information regarding the location and the internal diameter of the perforator to be cannulated. During dissection of the flaps, we anyway divide the proximal perforators. One of such perforator was identified under loupe magnification and skeletonized for the study. Therefore no harm was done to the patient. The artery was separated from the venae commitantes. The P-50 polyethylene microcannula was passed gently into the proximal loop of the artery. Free flow of arterial blood through the cannula confirmed the proper cannulation. The blood sample was taken for measurement of arterial blood gases so as to confirm the placement of the cannula in an artery rather than a vein. The cannula was then connected to the precalibrated physiograph, which was used in the experimental model. Recordings were then taken which were calculated by the equations as mentioned for the different sensitivities, in experimental model (10).

Thus we measured the perfusion pressure in a perforator of known internal diameter and found that they were directly proportional to the internal diameter. The perforators were classified depending upon the internal diameter as small (1.2 mm or less), medium (1.3–2.0 mm) and large (more than 2.0 mm). In small, medium and large sized perforators the range of perfusion pressure was 20–25, 20–33 and 32–49 mmHg, respectively.

Microcirculation :

Anatomy of text books do not stress the importance of the vascularity of the deep fascia except for its structural constituents and functional ability to cover the muscles. Histologic study proved the existence of subfascial and suprafascial network.

The rich vascular network in the deep fascia have been emphasized by various scientists, but the actual demonstration of live circulation in the deep fascia has not been previously witnessed. Encouraged by the sight of *live circulation in the web membrane of toad hind limb in experimental model*, a successful attempt was made to demonstrate the live circulation in the vascular network of the human deep fascia. Fascial extension of inferiorly based fasciocutaneous flaps were dissected in patients with distal leg and heel defects (11). The fascial extension in continuity with a proximal retrograde fasciocutaneous flap was mounted on a glass slide under natural tension and examined under a microscope under 150X and 600X magnification (Fig.8). The anastomotic channels and circulation could be seen clearly in both layers. *We witnessed live microcirculation and the movement of individual red blood corpuscles in the vascular channels of the deep fascia* (Figs. 9a & b). In a field of observation, there were single or multiple vessels, vascular wall was well delineated, blood was flowing in a high speed, individual cells could be seen moving. We also noticed that the deep fascia has two layers with circulations that are independent of each other. A video recording was done to document these important features. This study led us to understand the intensity and magnitude of microcirculation associated with the deep fascia and to prove the rationale for incorporating the deep fascia to provide safety to the flap. This also explains why flap of large dimensions can be transferred

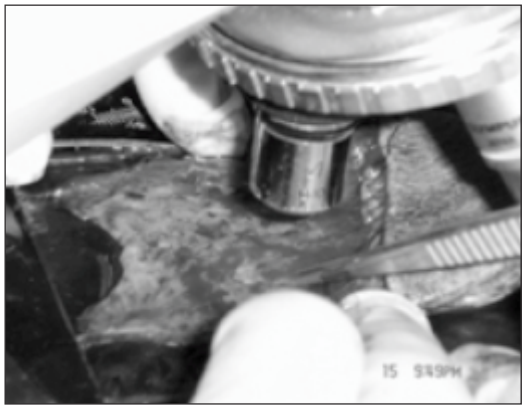

Fig. 8 : The fascial extension in continuity with a proximal retrograde fasciocutaneous flap was mounted on a glass slide under natural tension and examined under a microscope under 150 X & 600 X magnifications.

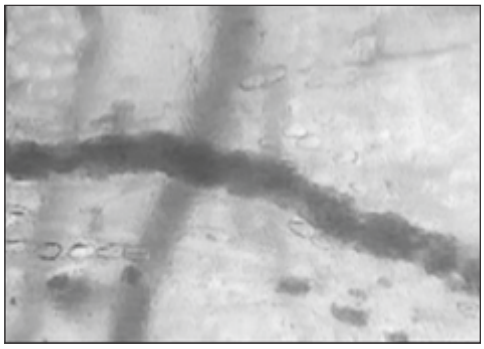

Fig. 9 (a) :

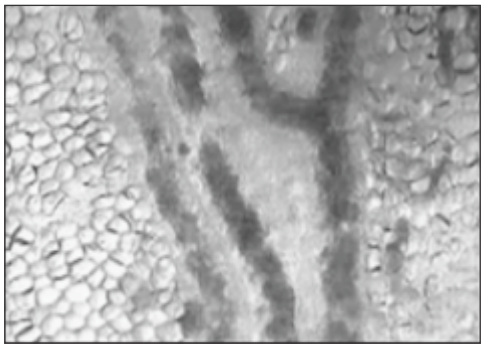

Fig. 9 (b) :

a&b- Photomicrographs showing multiple vascular channels in the deep fascia.

for reconstruction of defects exposing underlying vital structures. Such vascular network exists in every tissue of our body with blood flow. However we cannot demonstrate live circulation in them as they are thick tissue and demonstration of circulation is only possible in transparent tissue which can be observed under the lance of the microscope.

Lymphatic circulation :

It is well known that vascular arcade and lymphatic network co-exist all over the body with distinct physiological functions complimentary to each other. We visualized lymphatics in the deep fascia under electron microscope with 4000 magnification. Encouraged by our previous research of demonstration of live microcirculation in the deep fascia, we successfully explored the possibility of demonstrating live lymphatic circulation. Using the same clinical model, we examined under microscope using 600 magnifications (12). *We witnessed live microcirculation as well as live lymphatic circulation in the same field of observation with specific characteristics (Figs. 10 & 11).* A video recording was made to document these important

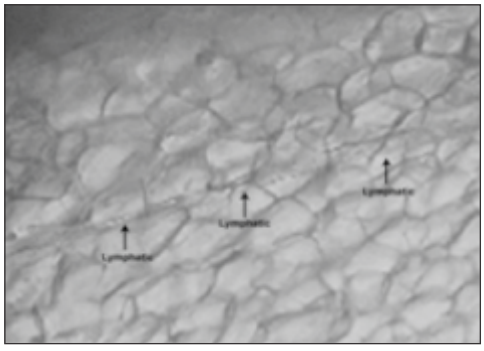

Fig.10 : Thin walled lymphatics containing straw colored lymph with suspended large molecules of fat and protein.

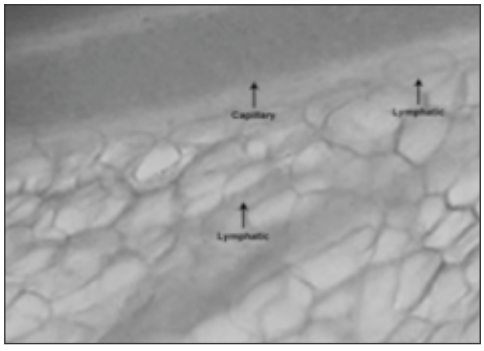

Fig.11: The caliber of the vessel is 20-25 times more than the lymphatic caliber.

features which to the best of our knowledge is not mentioned in the literature. The rich vascular network in the deep fascia can be easily witnessed by naked eye when ever any surface (supra or subfascial) of the deep fascia is observed during various surgical procedures. However the lymphatic system cannot be seen in routine histology or by naked eye. It was an exciting experience for the entire team to witness vibrant live microcirculation and lymphatic circulation in the deep fascia. Microphotography and video recording were performed. It was interesting to compare the live lymphatic circulation and live microcirculation in the same field of observation.

There were several interesting findings:

(1) In the same field the circulation in blood vessels (capillaries and arterioles) and lymphatics could be seen.
(2) The caliber of the vessels were 20-25 times more than the lymphatic.
(3) The wall of the lymphatics were thinner.
(4) The content of lymphatic was light straw colored with suspended large molecules of fat and protein (lymph) as compared to the red content of blood in the vessels.
(5) The rate of flow of lymph was much slower in lymphatics than rapid blood flow in the vessels.
(6) Depending upon the network, the flow in the lymphatics could be in different directions in the multiple channels in the same field.
(7) At places the lymphatic crossed over a vessel proving it to be a different system.
(8) Due to the variation of thickness of the wall of vessels and lymphatics, it was difficult to distinctly focus both the systems simultaneously at 600 magnification.
(9) In still photography the lymphatics almost simulate the septas separating the fat globules making it difficult to distinguish them. However the lymphatics are continuous channels and septas are around fat globules separating them having segmental appearance.
(10) Therefore only live lymphatic circulation can precisely identify these features.

Based on these informations emerged the supporting role of the lymphatics in tissue transfer. The gradual reduction in edema of the flap can be correlated with the lymphatic circulation as one of the major component. This further proves that inclusion of deep fascia in a flap has immense beneficiary effect.

Conclusion :

The successful tissue transfer in reconstructive surgery is based on strong rationality. The dynamics of circulation has two parts

(a) The supplying vessels (perforators) and
(b) The dense vascular network in different tissue planes. This presentation deals in detail about the perforators arising from the main vessels and their visualization through several clinical parameters. Through original research it also establishes, the vascular network

associated with the deep fascia and the live microvascular and microlymphatic microcirculation in it. We could also establish that the deep fascia consists of two layers which have individual vascular network and circulation. All these information are of immense value in the field of reconstructive surgery.

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