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MENOPAUSE AND HRT

All women who live beyond the age of 55 to 60 yr and many of a younger age, experience a period of transition from the reproductive to the nonreproductive stage of life, of which the most striking feature is the cessation of menstruation *ie* the menopause. Menopause is defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity.[1] The mean age at menopause has remained constant at 50, despite increase in longevity. In developed countries,where women have a life span of more than 75 yr the postmenopausal years comprise one-third of a woman's life. By the year 2000, the average life expectancy for women in developing countries is expected to be 65 to 70 yr[1]. The worldwide population of postmenopausal women is expected to be 1.2 billion by the year 2030, of which 76 per cent will be living in developing countries[2]. This sharp increase requires serious consideration of the health needs of this age group in developing countries. Although the term menopause and climacteric have generally been used interchangeably, menopause refers to a woman's last physiologic bleeding episode and is only part of the climacteric. The climacteric (or perimenopause) is the period of transition from the reproductive to the nonreproductive stage of life and thus, usually begins several years before (premenopause) and extends for a number of years (postmenopause) after the menopause. The climacteric is characterised endocrinologically by evidence of decreasing ovarian activity, biologically by decreasing fertility and clinically by alterations in menstrual pattern and by a variety of symptoms.[1]

Demography

The median menopausal age is 50-51 yr with a range of 39 to 59 yr[3]. Undernourished women appear to have menopause 4 yr earlier compared with those who are not. Of all the known possible risk factors associated with menopause, cigarette smoking is perhaps the most well documented. Smokers have menopause on an average one to two years earlier than non-smokers. No other factors have been consistently related to menopausal age. Reproductive history, including early menarche, parity, upper socio-economic class, higher educational status and oral contraceptive use have been suggested to be associated with later menopause, but the associations have not been consistent.[4]

The menopause is defined to be premature if follicular regression occurs before the age of 40 yr.[5] Women who experience premature menopause, either spontaneously or following surgery or radiotherapy are more prone to the distressing symptoms and long-term sequelae of the menopause.

Endocrine Changes during Climacteric

Menopause occurs due to ovarian senescence which occurs due to exhaustion of ovarian follicles. Oogenesis starts as early as the third week of gestation, reaches a maximum at twentieth week and subsequently declines till menopause. The foetal ovary contains approximately 7 million primordial follicles which reduces to 2 million

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175
22/5/98

at birth and approximately 3,00,000 at puberty. Ninety per cent of primordial follicles undergo atresia and only 10 per cent ovulate *ie* approximately 400 ovulations in a woman's reproductive life.[6] The ageing ovary reflects the decreasing capacity of the residual follicles to secrete estradiol which decreases from 300-500 pg/ml to less than 25 pg/ml.[5] In postmenopausal women estradiol is derived primarily from the peripheral aromatization of androstenedione to estrone to estradiol, which increases from 1 per cent in premenopausal to 1.5-4 per cent in postmenopausal women.[7] This androstenedione is also converted to testosterone. Decreasing estradiol levels and increase in ovarian testosterone increase the androgen/estradiol ratio[8]. The decreasing levels of estradiol result in 10-20 fold (*ie* 75-200U/1) increase in FSH, and 2-3 fold (*ie* 60-90U/1) increase in LH.[7,9] Excessive increase in FSH is also due to lack of inhibin secretion by the ovary which has a FSH suppressive action.[10] The periodic pulsative releases of FSH and LH are due to increased responsiveness of pituitary to gonadotrophic releasing hormones. Later in menopause the FSH and LH levels decrease but still remain above the fertile cycle levels. Progesterone levels also decrease. A decline in serum prolactin levels consistent with decreasing estrogen is also seen.[8]

Menstrual Pattern during Climacteric

The falling levels of estrogen result in menstrual changes. As women come closer to the menopause, menstrual periods often become irregular and are usually less frequent. In some women there is transient polymenorrhoea, mainly due to a reduction in the follicular phase. The menopausal transition–*ie* the time from the onset of irregularity of the menstrual cycle to the final menstrual period–lasts for an average of 3.8 yr.[11]

Short Term Symptoms

At climacteric, ovarian estrogen and progesterone production fall to low levels which in some women is associated with a series of signs and symptoms due to the physiological consequences of sex steroid deficiency. Deficiency of estrogens may result in atrophic changes in the genital tract leading to vaginal dryness, atrophic vaginitis, dyspareunia and the development of vasomotor manifestations such as hot flushes, excessive perspiration, palpitations, headache and vertigo. The women may also suffer from psychological symptoms such as increasing nervousness, apprehension, lack of concentration, irritability, depression and insomnia. These symptoms comprise the menopausal syndrome. The prevalence of menopausal syndrome varies widely not only between individuals in the same population, but also between different populations.Also, it has been difficult to distinguish between symptoms that result from loss of ovarian function and those from the ageing process or from socio-environmental stresses of the mid-life years. Some of the more common symptoms are described below.

Vasomotor symptoms

Hot flushes, night sweats, insomnia, palpitation and headaches are usually attributed to vasomotor instability. Of these, the hot flush is the specific symptom of the menopause. The hot flush is described as a sudden reddening of the skin over the head, neck and chest and is experienced as an explosion of heat followed by profuse sweating. The flushes usually last from a few seconds to several minutes. They occur at varying intervals from every 10-30 minutes to once a week or more.[12] They occur more frequently at night. Insomnia usually occurs as a secondary effect of sleep disruption caused by night sweats.[11]

The prevalence of hot flushes associated with menopause varies in different cultures. For example, the prevalence has been reported to be nil in Mayan women, 10-22 per cent in Hong Kong women, around 17 per cent in Japanese women, 23 per cent in Thai women, 45 per cent in North American women and up to 80 per cent in Dutch women. Although some studies have shown inconsistencies in the reported prevalence of these symptoms, in general, flushes and sweats are more common in European and North American women than in other populations. A high intake of dietary phytoestrogens (estrogen like compounds found in plants) has been suggested as a possible explanation of the lower frequency of menopausal symptoms in Japanese as compared with Caucasian women.[11]

Recent studies [13] suggest that menopausal symptoms occur due to an imbalance of the endogenous opioid system. Endogenous B-endorphin and other opioids regulate nuclei in the brain stem which in turn may influence not only the temperature regulating centre but also vessel wall functions. The endogenous opioid system is regulated by several factors and after some time a new equilibrium is achieved and symptoms subside.

Urogenital atrophy

The epithelium of the vagina and of the urethra and bladder respond to estrogens. If estrogen concentrations are insufficient, these tissues atrophy. The

vaginal epithelium loses its normal rugose appearance and becomes attenuated, pale and transparent. The depth of the vaginal vault is shortened and the upper third begins to constrict. Atrophic vaginitis can result from marked atrophy of the lining of the vagina. Vaginal atrophy can cause vaginal dryness, burning, pruritis, dyspareunia and prolapse.The pH of the vagina increases, thereby promoting the growth of bacteria which may result in vaginal infection. Atrophy of the mucosa of the lower urethera and bladder may lead to urinary symptoms such as urgency, frequency, dysuria, nocturia, incontinence, as well as the development of urinary tract infections.

A Swedish study [14] that interviewed 900 menopausal women found that 29.2 per cent complained of urinary incontinence, 13 per cent gave history of repeated urinary tract infections, 15 per cent complained of pruritis and vaginal discharge and 38 per cent had vaginal dryness and dyspareunia. Loss of interest in sexual relations was found in 32.7 per cent of women. There is marked variability in the onset and severity of atrophy of the urogenital tissues. This is in part due to variations in the rate of decline of estrogen production, which may be acutely or chronically muted by factors that increase either prehormone production or efficiency of conversion of prehormone to estrone. Some women may become symptomatic in months, others may take years to develop symptoms or urogenital atrophy, and some may never develop such symptoms.

Other complaints

Some frequently mentioned symptoms of menopausal syndrome are depression, irritability, nervous tension, palpitations, headaches and fatigue. Changes in B-endorphins and other opioids that occur during this period lead to an influence in the nervous transmitters of the GABA - system and serotonin system .[13] These changes may explain in part why many women experience psychic and psychologic symptoms around the menopause. Thining of skin, loss of hair and brittle nails are also some of the changes evident during this period. However, it is unclear to what degree each of these symptoms is related to estrogen withdrawal, ageing and or environmental stress.

Studies are ongoing at the Institute for Research in Reproduction (IRR), Mumbai, to evaluate the prevalence of menopausal symptoms in women in an urban setup and to determine their attitude towards hormone replacement therapy.(HRT). Climacteric women attending the Family Welfare Clinics of IRR were interviewed with the help of a precoded questionnaire. Data collection included age at menopause, menstrual history during the transition period, vasomotor and genitourinary symptoms, history of sexual activity and frequency and their attitude towards HRT. Preliminary analysis of responces of 100 perimenopausal women revealed that the mean age at menopause was 45.08 yr. The age of the women interviewed ranged from 40 to 60 yr. Hot flushes, sweating and insomnia were complained of by about 25 per cent of women. The most frequent complaints in this age group were fatigue and muscle-joint pain (48%); 84 per cent of women interviewed were not aware about HRT. When asked whether they would be willing to take long-term HRT, only 16 per cent of women agreed . The common reason for refusal to take treatment was on account of vaginal bleeding (34%), while 15 per cent felt that menopause is a normal phenomenon and hence no treatment should be taken.

Management of the Menopause

During the current decade, the management of menopause will become a national health concern as millions of baby boomers reach this stage of life. Medical intervention at menopause should be regarded as a programme of preventive health care in the same category as family planning. In this context HRT has found its place in the treatment of symptoms and some harmful effects of menopause.

In general, there are three indications for which HRT is used . These are (i) vasomotor and genitourinary symptoms related to estrogen deficiency, (ii) prevention of osteoporosis *eg* estrogen therapy reduces the rate of bone mass loss in postmenopausal women to the premenopausal rate thus reducing the number of fractures, and (iii) prevention of cardiovascular morbidity and mortality. To derive maximum benefits of HRT for prevention of osteoporosis and cardiovascular disease, treatment should be started at menopause and continued for at least 5 to 7 yr.

There are many controversial issues surrounding this therapy due to conflicting data from epidemiological studies *viz.* (i) what hormonal agent or route of administration is best? (ii) what is the best regimen, sequential or continuous? (iii) how long to continue the therapy? (iv) should very old women be started with HRT? (v) does HRT increase the risk of cancer? *etc.*

Hormone Replacement Therapy

Estrogen can be given in a variety of routes. In practice, the oral, transdermal, subcutaneous and vaginal routes are commonly employed. Each has benefits and disadvantages. Selecting the appropriate drug and route and also duration of therapy would depend on whether the woman desires long-term systemic treatment for the premature or sequelae of menopause or wishes to merely have relief of climacteric symptoms, whether she is willing to experience bleeding, the presence or absence of uterus, the presence or absence of risk factors or osteoporosis, cardiovascular disease, the availability and cost of the preparation.

Oral HRT

Synthetic estrogens (ethinyl estradiol) are not used for HRT because of their enhanced thrombogenic effect. Natural estrogens are used. Oral estrogen preparations are relatively inexpensive, easy to administer and easy to discontinue. The disadvantages are that some women experience nausea and compliance cannot be guaranteed. Oral ingestion produces a first pass hepatic effect. Although no increased risk of venous thrombotic disease has been documented it may be prudent to use transdermal estrogen in women who have experienced deep vein thrombosis. The commonly used oral natural estrogens are estradiol valerate, conjugated equine estrogen (main component is estrone sulphate) and piperazine estrone sulphate. (Table I).

Table I. The commonly used estrogen preparations for HRT

Oral	Estriol succinate 2 mg (Evalon)
	Estradiol valerate 2 mg (Progynon)
	Conjugated equine estrogen, 0.625 mg, 1.25 mg (Premarin)
Transdermal	Estradiol (Estraderm TTs 50,100 µg)
Subcutaneous	Estradiol (25, 50, 100 mg.)
Vaginal	Conjugated equine estrogen 0.625 mg in 1 g base (Premarin)
	Estriol 0.1 per cent (Ovestin)

HRT - hormone replacement therapy

Progestogens

When estrogen alone is taken for a long time, there is risk of endometrial hyperplasia and endometrial carcinoma. The risk is related to both the duration and dose used. Progestogen supplementation for about 12 days in each month restricts endometrial proliferation and ensures periodic transformation of a proliferative endometrium into a secretory one. The progestogen commonly used sequentially for 12 days each month with the protective doses for endometrium per day are listed in Table II.

Table II. Protective doses of progestogen for HRT

Progestogen	Protective dose
Dydrogesterone (Duphaston)	20 mg
Medroxy progesterone acetate (Provera, Farlutal)	10 mg
Norethisterone (Micronor)	1.05 mg
Levonorgestrel (Neogest)	150 µg

Unfortunately the addition of cyclical progestogen leads to withdrawal bleeding and premenstrual syndrome like fluid retention, breast tenderness, irritability, headaches and depression. The androgenic progestogens (norethisterone and levonorgestrel) will lower the concentration of HDL cholesterol. If the daily progestogen dose is reduced to norethisterone 1 mg and levonorgestrel 150 µg, the changes in lipid profile are minimal. Estrogen and progestogen may be prescribed separately or as a combined preparation (Table III). In a woman with an intact uterus if a combined preparation is not available a natural estrogen should be prescribed daily together with dydrogesterone or medroxy progesterone for 12 days of each calendar month. The compliance among postmenopausal HRT users may be poor because of heavy or prolonged withdrawal bleeding but the problem can be overcome. Progestogen therapy can be avoided in hysterectomised women.[5]

Table III. The commonly used combined preparation for HRT

Nuvelle	Estradiol valerate 2 mg Levonorgestrel 75 µg
Prempak C 0.625	Conjugated equine estrogen 0.625 mg Levonorgestrel 75 µg
Prempak C 1.25	Conjugated equine estrogen 1.25 mg Levonorgestrel 75 µg

Continuous combined regimen

The aim is to give continuous combined estrogen and low dose progestogen to render endometrium atrophic

ultimately inducing amenorrhoea. However, many women discontinue the use of this combination within first 6 months because of irregular bleeding. Continuous combined therapy is currently a subject of extensive research.

Tibolone

Tibolone has weak estrogenic, androgenic and progestogenic actions and may be used in postmenopausal women. The dose is 2.5 µg daily and is used mainly for the relief of vasomotor and psychological symptoms. However, 15 per cent of postmenopausal women have irregular bleeding. It is also expensive.

Non-oral HRT

There is no first pass hepatic effect and nausea is avoided. The transdermal estradiol patch is self adhesive and delivers estradiol over a period of 3-4 days at a constant rate of 50 µg per 24 h . One patch is applied twice a week on a dry hairless area of the skin, below the waist line. A new area should be selected for each application. The patch is easy to apply, easy to remove and has a short-half life. The drop out rate on account of local skin reaction is around 5 per cent. It is relatively expensive.

Subcutaneous estradiol implant

Subcutaneous pellets of crystalline estradiol release the hormone over a period of more than 6 months. The commonly used dose is 50 mg every 6 months which is adequate for bone conservation.

The disadvantages are that implantation requires a surgical procedure under local anaesthesia every 6 months and in case the woman wants to discontinue, it is difficult to remove the implant. A small number of women may have recurrence of menopausal symptoms despite adequate levels of serum estradiol. The anterior abdominal wall, about 5 cm above and parallel to the inguinal ligament is the common site for the insertion of pellets.

In the presence of an intact uterus the patient needs to take oral progestogen for 12 days in a month along with non-oral HRT.

Vaginal estrogen

The therapy is useful in women who have been postmenopausal for some years and wish to have relief of vaginal dryness, atrophic vaginitis, urethritis or dyspareunia. The commonly available vaginal creams are conjugated equine estrogens (0.625 mg in 1 g of base and estriol 0.1%).

Non Hormonal Therapy

In the last decade, efforts have been directed to find non-hormonal alternatives to prevent postmenopausal osteoporosis for women who prefer not to use hormones or where estrogen is contraindicated. These include:

(i) A moderate level of physical activity especially weight bearing exercise appears to have a beneficial influence on peak adult bone mass although it does not prevent osteoporosis.

(ii) Calcium is an essential element for normal bone health. A life long supplementation with calcium in a dose of 800 mg/day is recommended as complementary therapy. Calcium intake in childhood and adolescence may be a determinant of peak bone mass. Calcium does not substitute for estrogen in preventive therapy in postmenopausal women. Vitamin D helps calcium absorption in the gut and reduces the rate of bone loss .[15]

Certain vitamins (B1, B2, B6, B12, Vit.A, Vit C, Vit.E) along with minerals have been shown to be effective in alleviating the menopausal symptoms *eg* hot flushes, palpitation, depression, anxiety, *etc.*

(iii) Calcitonin is effective in prevention of bone loss, but it is expensive and is only available as nasal spray and in injectable form.

(iv) Sodium fluoride has been known to increase bone density but studies are limited due to its adverse effects.

Osteoporosis and Estrogen Replacement

Osteoporosis is characterised by decreased bone mass and increased susceptibility to fracture most commonly of the wrist, the spine and the hip. Estrogen replacement therapy is very effective in preventing osteoporosis and reducing the risk of the associated fractures.

For conservation of bone in a well built, menopausal woman with no risk factors, the minimal effecitve dose of estradiol valerate is 2 mg and of conjugated equine estrogen is 0.625 mg daily. The minimal effective daily dose for bone preservation in a small built, thin, sedentary regular alcohol/tobacco user who has undergone bilateral

oopherectomy is likely to be higher and these factors must be borne in mind while prescribing HRT.

The greatest benefit is obtained if HRT is given shortly after the menopause prior to significant bone loss. However, there is clear evidence that in all stages of the post menopausal life HRT prevents bone loss. Five years of appropriate HRT reduces the lifetime incidence of the fracture femur neck by 50 per cent and of vertebrae to a greater extent[16]

Cardiovascular System and HRT

Mortality from coronary heart disease (CHD) like myocardial infarction among women increases with advancing age. Changes in serum lipids after the menopause suggest a relationship with estrogen deprivation. Total serum cholesterol decreases. Several epidemiological studies have demonstrated that with 4 or more years of oral estrogen therapy in both normotensive and controlled hypertensive women, the risk of CHD is reduced by more than 50 per cent as compared to " never users". There are no data available on CHD and HRT from developing countries.

Mechanisms of action of estrogen for cardioprotection

A 35 per cent reduction of LDL cholesterol results in a 50 per cent reduction in cardiovascular disease. However, estrogen reduces LDL cholesterol by only 10 per cent. This may explain about a third of the cardioprotective effect of estrogens. It also increases HDL which is believed to be protective against arteriosclerosis. Estrogen also increases the coronary blood flow as demonstrated by many angiographic studies. It also acts as an antioxidant and there is a favourable effect on haemostasis. Unlike synthetic estrogens, natural estrogens do not have any significant effect on the blood pressure. In only 2 or 3 per cent of HRT users there is an increase in blood pressure.[17]

When Should Treatment With HRT Begin ?

In the past women over the age of 60 yr have been denied HRT in the belief that they are too old and their skeleton is too osteoporotic to benefit from estrogen replacement therapy. Recent studies[18] using conjugated equine estrogen 0.625 mg daily plus calcium showed an increased bone density in both the spine and the femur neck after two years of treatment. Garnett *et al* [19] reported similar benefits with 75 mg estradiol implants in women over 60 yr of age after one year of treatment. The increase in bone density was greater in women who had more severe disease and it was concluded that implants are more effective in the treatment of established osteoporotic disease. In the elderly woman with osteoporotic fracture, hormone therapy is advocated as it decreases the risk of further fracture.

In fact Black[20] has convincingly argued for delaying the start of HRT for prevention of osteoporotic fractures. Reasons given for waiting until a later age include (i) the possibility that hip fracture risk can be more precisely estimated at 65 or 70 yr than at 50 yr of age; (ii) that treatment duration will be shorter and therefore, more cost effective if begun later; and (iii) the uncertainity associated with long-term treatment can be eliminated.

HRT and the Risk of Cancers

Breast carcinoma

Epidemiological studies on the risk of breast carcinoma are to some extent contradictory. The overall message is that extended use of estrogen therapy entails an increased risk being 1.3 - 1.6. The risk increases with the duration of therapy. Patients who develop breast carcinoma after estrogen therapy are usally detected with early stage tumours probably due to the close monitoring which they undergo during therapy. Women with a strong family history of the disease may be at a higher risk for developing breast carcinoma after estrogen therapy. Progestogens do not appear to have any protective effect. Breast cancer surveillance is recommended for women taking hormones at the same frequency as women not taking hormones. They should have regular breast examination and regular three-yearly mammography from the age of 50 years. [21]

Endometrial hyperplasia and carcinoma

Estrogen use of 10-15 yr may have increased risk of endometrial hyperplasia and carcinoma (RR 10) compared with women who have never used it but declines once estrogen is stopped. Use of progestogen along with the estrogen reduces the risk of endometrial cancer. Indeed the action of progestogen counteracts the cancer inducing effect of the estrogen on the endometrium. [11]

Endometrial screening in HRT users

If on transvaginal ultrasonography the endometrial thickness is more than 4 mm, there is a need for tissue sampling either by biopsy or by dilatation and curettage.

For patients on continuous combined therapy, screening is recommended generally once a year.

Studies of ovaries in Europe and North America show no additional risk of ovarian cancer. No information is available from developing countries. Several studies to find a link between HRT and cervical cancer were undertaken but results have been inconclusive[11].

There is no evidence that one form of estrogen is superior to another.

To summarise, it is known that short-term treatment of menopausal women with HRT for the symptomatic relief of climacteric complaints is effective, safe and generally well accepted. However, use of long-term HRT (for 7 yr or more) is still controversial. In clinical practice, the beneficial effects of long-term HRT on women's health, mainly on osteoporosis and cardiovascular disease, must be carefully weighed against a possible increased incidence and mortality from breast cancer. It is necessary to provide accurate and individual information to women about the advantages and disadvantages of using HRT. Educating potential users will enhance compliance, especially if women make this decision themselves, fully informed by their physicians. Women who agree to take HRT should have careful follow up monitoring so as to obtain maximum benefit for this therapy while minimizing any risks or side-effects.

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ICMR NEWS

The following meetings of various technical groups/ committees of the Council were held at New Delhi:

Meetings of Project Review Committees (PRCs) and Task Force (TF):

PRC on Cardiovascular Diseases, Ophthalmology, Urology and Gastroenterology	December 12, 1997
Sub-group of PRC on Hepatitis	December 16, 1997
PRC on Malaria, Filariasis and Leishmaniasis	December 19, 1997
TF on Child Psychiatry	January 15, 1998

Participation of ICMR Scientists in Scientific Events:

Dr. V. Kumaraswami, Dy. Director, Tuberculosis Research Centre, Chennai; Dr. B.V. Babu, Sr. Research Officer, Regional Medical Research Centre, Bhubaneswar; and Dr. K.D. Ramaiah, Sr. Research Officer, Vector Control Research Centre, Pondicherry, participated in the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases meeting on Social Science Methods for Community Directed Treatment at Mukuno, Uganda (November 17-21, 1997).

Dr. Poonam Salotra, Sr. Research Officer, Institute of Pathology, New Delhi, participated in the X Anniversary symposium of International Centre for Genetic Engineering and Biotechnology on Molecular Biology and Biotechnology for Development at Trieste, Italy (November 25-27, 1997).

Dr. M.D. Gupte, Director, Institute for Research in Medical Statistics, Chennai and Officer-in-Charge, CJIL Field Unit at Avadi, Chennai, participated in the meeting and discussion regarding the Study on Posterior Tibial Nerve Decompression at Bologna, Italy (December 8-14, 1997). He also participated in the meeting of the Sub-committee of the WHO Steering Committee on Special Action Project to review proposals for the treatment of paucibacillary leprosy with a single dose of rifampicin, ofloxacin and minocycline and the seventh meeting of SAPEL Steering Committee at Geneva (December 14-16, 1997).

Workshop on Intellectual Property Rights:

The second ICMR-TIFAC (DST) Workshop on Intellectual Property Rights was held at the Desert Medicine Research Centre (DMRC), Jodhpur on December 12, 1997. Besides scientists of DMRC, scientists from several other Jodhpur-based R&D Institutes also participated in this Workshop.

This is the second in the series of Workshops jointly conducted by the Patent Facilitating Cell of the Technology Information, Forecasting and Assessment Council (TIFAC), an autonomous body of the Department of Science and Technology, New Delhi and the ICMR. The first Workshop was held at the National Institute of Occupational Health (NIOH), Ahmedabad on August 13, 1997. Scientists from the NIOH, and the ICMR Institutes located in the Western region of India *viz.*, IRR, IIH, EVRC, GRC, Mumbai and NIV, NARI, Pune also participated. This orientation programme on emerging issues of patents and related areas will cover all the ICMR institutions in a phased manner.

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
LXXXV Session of the Indian Science Congress	January 3-7, 1998; (at Hyderabad)	Dr. P.K. Sai Prakash, Local Secretary of the Indian Science Congress, Department of Chemistry, University College of Science, Osmania University, Hyderabad-500007.
VI Annual Meeting of the Molecular Immunology Forum-1998	January 12-14, 1998; (at New Delhi)	Dr. H. Krishna Prasad, Convenor of MIF-1998, Department of Biotechnology, All India Institute of Medical Sciences, New Delhi-110029.

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
International Conference on Changing Patterns of Health in Developing Countries	January 21-23, 1998; (at Vadodara)	Dr. Jayasree De, Head, Department of Geography, M.S. University of Baroda, Vadodara-398002.
Update Ayurveda '98	February 9-14, 1998; (at Mumbai)	Dr. S.A. Dahanukar, Professor, Department of Pharmacology, Seth G.S. Medical College, Mumbai-400012.
Workshop on Application of Iontophoresis, Sonophoresis and Hyperthermia in Drug Delivery	February 27-28, 1998; (at Manipal)	Dr. N. Udupa, In-charge Principal and Professor, College of Pharmaceutical Sciences, Manipal-576119.
International Conference on Nonlinear Dynamics and Brain Functioning	February 5-11, 1998; (at Bangalore)	Dr. N. Pradhan, Convenor of the Conference, Department of Psychopharmacology, National Institute of Mental Health & Neurosciences, Bangalore-560029.

COUNCIL'S TRAINING PROGRAMMES FOR 1998-99

Leprosy

At the Central JALMA Institute for Leprosy, Agra:

- Multidrug Therapy Orientation Course in Leprosy for Medical Officers (April 6-17, August 17-28, October 26-November 6; and December 7-18, 1998).

Virology

At the National Institute of Virology, Pune:

- Diploma in Medical Virology (July 1998-May 1999).

At the Enterovirus Research Centre, Mumbai:

- Workshop on Isolation and Identification of Polioviruses (January 19-29, 1998).

Reproductive Biology

At the Institute for Research in Reproduction, Mumbai:

- Workshop on Andrology for Clinicians (November 16-30, 1998)

Endocrinology

At the National Institute of Nutrition, Hyderabad:

- Annual Certificate Course on Endocrinological Techniques and their Applications (August 1-September 15, 1998).

Nutrition

At the National Institute of Nutrition, Hyderabad:

- M.Sc. in Applied Nutrition (June 1, 1998-February 28, 1999).
- Postgraduate Certificate Course in Nutrition (December 1, 1998-February 28, 1999).

Laboratory Animal Technology

At the National Centre for Laboratory Animal Science, National Institute of Nutrition, Hyderabad:

- Training Course for Laboratory Animal Technicians (June 16-July 31, 1998).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

- Orientation Course on Occupational Health for Industrial Medical Officers (February 17-28, 1998).
- Training Course on Environmental Hygiene Practice (November 16-20, 1998).

Biomedical Statistics

At the Institute for Research in Medical Statistics, Chennai:

- Basic Course in Statistics for Postgraduate Medical Students (July 1998).
- Basic Course in Statistics for Medical Officers (November 1998).

GUIDELINES FOR EXCHANGE OF HUMAN BIOLOGICAL MATERIAL FOR BIOMEDICAL RESEARCH PURPOSES

F.No. L. 19015/53/97-IH (Pt.)
GOVERNMENT OF INDIA
Ministry of Health & F.W.
Department of Health
Nirman Bhawan
NEW DELHI

the 19th November, 1997

OFFICE MEMORANDUM

Subject : Guidelines for Exchange of Human Biological Material for Biomedical Research Purposes.

The Ministry of Health & Family Welfare issued an Office Memorandum No. L. 20025/90/90-F, dated 27th February, 1992 which permitted the restricted transfer of biological material abroad under certain circumstances for research/ diagnostic purposes. The Office Memorandum also indicated that the Director-General, ICMR, would be the nodal point to clear all such proposals.

2. The need for revised/expanded guidelines has been felt over the past two years. Accordingly, the Ministry of Health & Family Welfare have taken necessary steps in this regards.

3. The revised guidelines in respect of HUMAN BIOLOGICAL MATERIAL, in supersession of this Ministry's Office Memorandum No. L. 20025/90/90-F, dated 27th February, 1992 are prescribed as under :

I. Definition

Human material with potential for use in biomedical research :

Organs and parts of organs; Cells and tissues; Sub-cellular structures and cell products; Blood; Gametes (sperm and ova); Embryos and foetal tissues; Wastes (urine, faeces, sweat, hairs, epithelial scales, nail clippings, placenta *etc.*); Cell lines from human tissues.

The sources of these materials could be from patients following diagnostic or therapeutic procedures, autopsy specimens, donations of organs or tissues from living or dead persons, foetal tissues, body wastes or abandoned tissues. Human material could also be held in tissue banks and used for research.

II. Transfer

Guidelines for considering requests for transfer of biological material abroad for research/diagnostic purposes and requests for transfer of biological material from abroad to Indian Institutions for research purposes :

(i) Exchange of material for diagnostic or therapeutic purposes for individual cases may be done without restriction, if this exchange is considered necessary by the doctor(s) in-charge of the patient. No permission needs to be sought from

(ii) Exchange of material from and to recognised laboratories such as WHO Collaborating Centres or WHO Reference Centres may be allowed as part of their routine activities relating to quality control, quality assurance, comparison with reference material *etc.*, without having to seek permission from any authority.

(iii) Where exchange of material is envisaged as part of a collaborative research project, the project proposal as a whole must be routed through the appropriate authorities (details under III below) for evaluation and clearance. The exchange of human material should be an integral part of a collaborative project, which should have been approved by the Institutional Review and Ethics Committees, and not be a separate activity.

(iv) The availability of facilities within India for carrying out certain investigations need not prevent collaboration with scientists in other countries for the same investigations including transfer of human material, if required.

(v) On the issue of technology transfer/training of Indian scientists abroad/training of foreign scientists and students in India, and visits by the foreign collaborators to their Indian partners' laboratories to work with Indian material, there should be no restrictions on the visits of scientists to the laboratories concerned. However, any field work to be undertaken in the community and other sensitive issues would have to be regulated according to the rules of the Government.

(vi) In order to protect the rights of the Indian study subjects as well as Indian scientists/organisations, Memoranda of Understanding and/or Agreements on Material Transfer should be entered into between the collaborating partners (Indian and Foreign). These should, according to the requirements of case under consideration, include items pertaining to identification of the collaborating or sending/receiving parties, background, the material to be transferred and its quantities, purpose of transfer, the research to be carried out using the material, confidentiality, intellectual property rights, filing of patents, arrangements for future commercial exploitation, reporting, publication rights, indemnification, termination of agreement, assignation or transfer of agreement/rights, safety norms to be observed, shipping arrangements, 'qualified user' information, and any other matter that may be relevant to the particular exchange of material.

III. Mechanism

Mechanism for processing requests for transfer of biological material abroad for research/diagnostic purposes :

(i) Agencies and departments such as ICMR, CSIR, ICAR, DBT, and DST could make use of these guidelines and take decisions accordingly on the requests from their respective institutions.

(ii) The Directorate-General of Health Services/Ministry of Health & Family Welfare could utilise the guidelines and take decisions on the requests from the DGHS/Health & Family Welfare Ministry administered institutions, as also on referrals, if any, from any other government agency/department not covered under (i) above.

(iii) Autonomous institutions and institutions of national stature such as PGIMER, Chandigarh; AIIMS, New Delhi; Sree Chitra Tirunal Institute of Medical Sciences & Technology, Thiruvananthapuram; and Sanjay Gandhi Postgraduate Institute of Medical Sciences, Luknow, and similar institutions of national stature, could be empowered to take decisions on their in-house proposals for foreign collaboration, by following the guidelines.

(iv) Private institutions engaging in collaboration directly with foreign institutions should send their requests to ICMR. If, however, they are also collaborating with an Indian institution as part of the collaborative programmes with a foreign institution (for example, between a private institution and CSIR lab. collaborating with a foreign institution), then the appropriate central agency (CSIR in the example cited) may decide on the request according to all relevant guidelines.

(v) Biomedical research project proposals for foreign collaboration from Medical Colleges, Universities and Institutions under the UGC may be routed through ICMR.

(vi) State health authorities may take the decision in respect of institutions under their administrative control.

(vii) All foreign collaborative projects in biomedical research (after scrutiny and decision by the respective agencies/ departments as described above from (i) to (vi) are to be placed before the Health Ministry Screening Committee (HMSC) for final endorsement. This would mean that all institutions, agencies and departments would have to send their proposals to the ICMR for obtaining such endorsement by the HMSC, as ICMR is the Secretariat for the HMSC at present.

(viii) It is essential for information to be available in a central location. This could be the secretariat of the HMSC, *i.e.* the ICMR Headquarters.

IV. Exchange of Biological Material for Commercial Purposes

Guidelines for exchange of biological material for commercial purposes :

The ICMR has been advised to set up a committee consisting of experts from relevant fields for deciding each proposal on a case-by-case basis and to furnish their views to the Government for consideration. The committee, in addition to biological material, will also consider proposals involving transfer of medicinal plants and biological molecules developed in the laboratories, after seeking inputs from the relevant experts, if such transfer is for commercial purposes and a proposal in this regard is received from the Foreign Investment Promotion Board (FIPB). A minimum of three months time would be required to process the FIPB proposals.

sd/-

(Ashok Mehta)
Under Secretary of the Govt. of India

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