

25 years of essential medicines

Medicines are as old as mankind but the era of modern medicines, as we know them, began only with the introduction of aspirin and the advent of the pharmaceutical industry in Germany, as a by-product of the chemical and dyestuff industry, at the turn of the 19th century.

In the intervening 100 years, drugs (when used as medicines rather than for recreational purpose) have become an indispensable component of healthcare and have proliferated in number, scope and variety. Researchers look at every conceivable source – plant, animal, human, mineral – in the search for newer and better therapeutic agents. Infections have been conquered or controlled, physically distressing symptoms have been ameliorated, mental illnesses improved substantially, and even cancers, genetic disorders and chronic multifactorial illnesses targeted by pharmacotherapy. In short, healthcare today is inconceivable without drugs.

The need now is to extend the reach of drugs to every corner of the globe, specially those individuals who belong to impoverished or marginalized sections of the global community. As the new millennium unfolds this has become one of the most pressing public health challenges facing the world.

25 years ago, on October 21, 1977, to be precise, the World Health Organization [WHO] launched the essential drugs program with this very goal in view. Essential drugs are those that satisfy the priority health needs of the community and therefore must be available at all times, in appropriate strengths and dosage forms, with assured quality, at affordable cost and backed by appropriate information. The WHO list of essential drugs has indeed been the model around which the drug policies of many countries have germinated and developed. The essential drugs concept is not a poor man's concept as the global community has realized. It restricts a clinician's choice of the best drugs for his patient or his right to individualize drug therapy no more than a textbook of medicine does. Rather, it is a very rational way to extend the benefits of drugs to the maximum number of patients in any setting where resources are limited, as most settings are. Admittedly, an essential drugs program may not be applicable to the individual patient who suffers from an uncommon disorder or fails to respond to standard treatment, but for the community it is an optimum solution and the only one that seems to be working at the moment.

Propounding the essential drugs concept is not enough. It is the duty of every government and every organization working in this field to ensure that people do have access to quality assured essential drugs at affordable cost in times of need. Many hurdles remain and new ones continue to appear – how to offset the effect of the ever-increasing rich-poor divide in the world, how to tackle the menace of counterfeit drugs, how to include more effective but costlier remedies in healthcare programs, and so on. The challenges must be met if 'health for all' is to become a reality.

The essential drugs program is one of the longest and most successful public health programs in the world has ever seen. It is also perhaps the most criticized. Fortunately criticism comes only if you work. Therefore, let us renew the pledge to continue the program which is as relevant today as it was 25 years back.

Avijit Hazra & Amitava Sen

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Hormone replacement therapy—the evidence so far

Joydev Mukherji

Use of hormone replacement therapy (HRT) is increasing worldwide as life expectancy increases and there is widespread perception that HRT not only relieves menopausal symptoms but can also prevent or treat chronic diseases such as cardiovascular disease (CVD) and osteoporosis. This widespread use stands in stark contrast to the dearth of conclusive data regarding the merits and demerits of HRT. There is thus an urgent need to critically appraise the available evidence to assess the balance of benefits and risks.

Although numerous observational studies generally have supported the use of HRT, data from several recent randomized trials¹⁻⁵ have challenged the prevailing rationale for prescribing HRT for prevention of CVD and have raised the possibility that it may actually lead to short-term risk escalation.

Short term effects of HRT

Regarding short-term use (< 5 years) for alleviating the menopausal symptoms of vasomotor instability and urogenital atrophy, there is far less controversy when compared to long-term administration and the benefit / risk equation.

Vasomotor symptoms

There is a clear reduction in vasomotor symptoms with HRT, most studies having duration of 12 months on average.⁶ A more recent 3 years randomized trial of estrogens and various estrogen/progestogen regimens versus placebo⁷ confirmed decrease in vasomotor symptoms of 72 to 83% at 12 months, an effect that was significantly reduced by 3 years.

Urogenital symptoms and libido

With regard to the lower genital tract, most evidence of estrogen-induced benefit comes from observational and case-control studies. A recent meta-analysis has however shown effectiveness of estrogen, regardless of the route of administration.⁸

Alleviation of incontinence is at best uncertain. Two recent meta-analyses^{9,10} have revealed a significant effect on subjective measures of symptomatology with no effect on objective measures of incontinence. In the face of inconclusive results, many clinicians use a trial treatment of estrogen for stress and urge incontinence. The Canadian Consensus on Menopause and Osteoporosis have recently stated in their recommendations that there is no objective benefit from Estrogen Replacement Therapy (ERT) in postmenopausal stress incontinence. Also there is neither objective nor subjective benefit from ERT for postmenopausal urge incontinence.¹¹

Although there is no evidence to support a direct effect of estrogen on libido,⁶ estrogenization of the vagina aids vasocongestion and lubrication leading

to relief of dyspareunia. There is no controversy about treatment of overt dyspareunia in postmenopausal women with vaginal atrophy.¹²

Psychological symptoms

A meta-analysis concluded that estrogen was effective in alleviating depressed mood.¹³ There is no evidence from randomized trials confirming that estrogen either elevates moods or treats proven depression.

Long term effects of HRT

Estrogen stops bone loss in early, late and elderly postmenopausal women by inhibition of bone resorption resulting in a 5 to 10% increase in bone mineral density (BMD) over 1-3 years.¹⁴⁻¹⁶ When HRT is stopped, bone loss probably resumes at the same rate as after the menopause.¹⁷⁻¹⁹ The fact that the reduction in fracture risk seems to be lost within 5 years of HRT withdrawal, irrespective of the duration of treatment, raises the issue of the optimum timing and duration of HRT.²⁰

Findings of several case-control and cohort studies²¹⁻²³ suggest HRT decreases the risk of hip fracture by about 30%, and results of two small placebo controlled studies,²⁴⁻²⁵ done in women with osteoporosis, suggest a 50% reduction in the risk of spinal fractures. The results of a meta-analysis²⁶ of 13 randomized placebo controlled trials suggest a 33% (95% Confidence Interval 45-98) reduction in vertebral fractures, and those of a meta-analysis²⁷ of 22 randomized trials indicate a 27% (CI 0.56-0.94, p = 0.02) reduction in non-vertebral fractures in a pooled analysis, with a 40% reduction for hip and wrist fracture alone. There have been no large placebo controlled trial of HRT in women with osteoporosis and with incident fractures as a primary end point; so the efficacy of postmenopausal HRT for prevention of osteoporotic fractures is much weaker than for other compounds (e.g. biphosphonates).²⁸

The long-term effect of HRT on cancer and cardiovascular disease have been debated since HRT was first prescribed. The need for objective data on long-term effects prompted the setting up of randomized controlled trials (RCTs) to study cancer and cardiovascular disease as end points - HERS,^{1,29,30,31} EVTET,³² WEST,³³ WHI,^{4,34} ESPRIT-UK,³⁵ and WISDOM.³⁶ Four of these trials,^{4,30,32,33} three of which were halted prematurely,^{4,32,36} have published their main result. The Women's Health Initiative^{4,34} study, which received wide-spread publicity, published results for part of the trial which was stopped early. In the WHI trial:

- Conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MP) were given to women with an intact uterus – stopped May, 2002.

- CEE only to hysterectomized women – ongoing and reports to be published in 2005.
- Trials with CEE and MP was planned to last 8.5 years but was stopped early as the number of cases of breast cancer had reached a prespecified safety limit and over all risks exceeded benefits. The average follow up was 5.2 years.

Reviewing the four published RCTs, including over 20,000 women followed for up to 4.9 years on average, the findings for seven major potentially fatal conditions that were primary or secondary outcomes are informative. These include cancer of the breast, endometrium and colorectum; coronary heart disease (CHD), stroke, pulmonary embolism; and fracture neck femur.

Overall, for women randomized to HRT compared with placebo, there was a significant excess of breast cancer (Relative Risk 1.27, 95% CI 1.03-1.56), stroke (1.27, 1.06-1.51) and pulmonary embolism (2.16, 1.47-3.18); a significant deficit of colorectal cancer (0.64, 0.45-0.92) and fracture neck of femur (0.72, 0.52-0.98); but no overall significant excess or deficit for endometrial cancer (0.76, 0.45-1.31) or CHD (1.11, 0.96-1.30).³⁷

Result from RCTs are similar to findings from observational studies for breast and colorectal cancer,^{38,39} as well as for venous thromboembolism (VTE),⁴⁰ and fracture neck femur. Increasing risk of breast cancer with duration of use in WHI study agrees with observational studies.³⁹ The WHI trial is the first RCT to confirm the increased risk of invasive breast cancer, the primary outcome, with combined HRT. Risk of VTE is greatest soon after starting HRT than in later years — another observational study finding corroborated.

Since the objective RCT data have confirmed previous observational data for these conditions, the evidence for a true effect are strong and unlikely to be due to bias or confounding.

It is when we come to the question of CHD, that our prevailing ideas of cardioprotective role of HRT receives a jolt. Many workers had argued that the lower rates of CHD among HRT users compared with non-users, found in observational studies, did not necessarily indicate that HRT was protective.^{34,38,40} It was the need for unbiased data on the incidence of heart disease that had prompted the setting up of most of the RCTs. For the first time results from HERS trial suggested an adverse effect of HRT on coronary disease in the first year after randomization.^{1,29} Finding from WHI showed the same trend, although not significant.⁴ One thing is certain — neither trial has shown long-term benefit for CHD.

The increased incidence of stroke among HRT is a new cause for concern. Result from previous observational studies had been inconclusive.⁴⁰

Beneficial effect from the WHI trial included a decreased incidence of hip and vertebral fracture by a third and colorectal cancer by 37% in active

group compared to placebo. The study was stopped after 5 years because the net level of risk was believed to outweigh the benefits. However, the overall level of risk are in all cases very small. For example for every 10,000 women treated with CEE and MP,

- An extra 7 women experience CHD event
- An extra 8 women experience a stroke
- An extra 8 women have VTE
- An extra 8 women have breast cancer
- In contrast, 6 fewer women will develop colorectal cancer and 5 fewer would suffer from hip fracture.

The WHI trial design did not consider conditions such as gall bladder disease, diabetes, quality of life and cognitive function.

Existing trials are too small to provide reliable information on other conditions such as ovarian cancer,⁴¹ or on cause specific mortality. As for Alzheimer's disease, the largest double blind randomized trials to date suggest that HRT does not slow its progress nor improves cognitive function.⁴² HRT probably has little effect on quality-of-life other than menopausal symptoms.⁴³

New results on about 12,000 women randomized to unopposed estrogen versus placebo are expected soon from ESPRIT-UK35 and part of continuing WHI.⁴ The data and conclusions for combined HRT reviewed here are, however, unlikely to change in the immediate future.

Result from WISDOM,³⁶ which was randomizing 22,000 healthy women to similar estrogen-progestin combination as WHI were due in 2012. This trial was also studying the effect of HRT on quality of life and cognitive function. The WISDOM trial team recently reviewed their project in light of the US experience. The UK Medical Research Council announced in October, 2002, that a decision had been taken to halt the WISDOM trial for scientific and practical reasons. The Independent International Committee was concerned by the slow progress of WISDOM and considered that the results would be unlikely to show a large reduction in the incidence of coronary heart disease (the chief concern).

Implications for practice

A risk-benefit evaluation on an individualized basis should be undertaken for all menopausal women considering HRT. Appropriate HRT with intention to treat short-term (2 to 4 years) for symptomatic control may be continued as in current practice. The longer term (over 5 years) use of HRT is more problematic, given the increased risk of breast cancer and adverse cardiovascular events (including coronary heart disease, stroke and venous thromboembolism). Combined HRT preparation is not the treatment of choice in preventing chronic conditions. The exception may be a woman with high risk for established osteoporosis who understands all the implications based on current data.

Should women stop taking CEE+MP? Not, if it makes them feel good, if they are at low risk from the negative effects, and they have reasoned after appraisal of the evidence with their physician why they do not wish to change. While many women have stopped or will stop taking combined HRT, cessation of all use is neither likely nor appropriate.

For women starting HRT, it would be recommended that the starting dose of estrogen be kept low over the age of 60. For example this could

be 1 mg. for oral, 50 mcg for transdermal 17 β -estradiol or 0.3 mg for conjugated estrogens. Meanwhile researchers can try to unravel the consequences of different treatment regimens. Doctors can offer advice, but ultimately only the women herself can decide.

In conclusion, a comparative benefit-risk summation for HRT is presented in the following table.

Table 1. Benefits and risks of long-term HRT in postmenopausal women

Degree of evidence	Benefits	Risks
Strong	<ul style="list-style-type: none"> • Relief of menopausal symptoms. • Prevention of bone loss. 	<ul style="list-style-type: none"> • Vaginal bleeding • Breast tenderness • DVT and pulmonary embolism.
Moderate	<ul style="list-style-type: none"> • Prevention of fractures. 	<ul style="list-style-type: none"> • Increased risk of breast cancer after long term use.
Weak	<ul style="list-style-type: none"> • Primary prevention of chronic heart disease. • Improvement of cognitive function and prevention of Alzheimer's disease. 	<ul style="list-style-type: none"> • Slight increased risk of endometrial cancer. • Slight increased risk of ovarian cancer.

CHD = Coronary heart disease; DVT = Deep vein thrombosis

Adapted from: Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet* 2002; 359: 2018-26.

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- **Couper MR, Mehta DK, editors. WHO Model Formulary. Geneva: world Health Organization, 2002.**

Recent public notifications from Central Drugs Standard Control Organization
 Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India,
 Nirman Bhawan, New Delhi – 110 011, Phone: 011-23018806, Fax: 011-23012648

On adverse drug reaction reporting

CDSCO, popularly known as the Office of The Drugs Controller General of India, has taken recent and welcome steps to strengthen the adverse drug reaction [ADR] monitoring activity in the country. To this end:

"CDSCO solicits the cooperation of healthcare professionals in collecting data of adverse events related to drugs marketed in India. The submitted data will be collated and evaluated by the National

Pharmacovigilance Center operating at The Department of Pharmacology, All India Institute of Medical Sciences, New Delhi – 110 029."

ADR data can be submitted by any healthcare professional on the predesigned 'Postal ADR Monitoring Form' downloadable in Adobe Acrobat portable document format from the CDSCO website at <<http://cdsco.nic.in>>. The 2-page form appears as follows:

POSTAL ADR MONITORING FORM
 National Pharmacovigilance Centre
 Department of Pharmacology
 All India Institute of Medical Sciences, New Delhi-110029, India

Name _____ Age _____ Sex _____
 Ward _____ Bed No. _____ DOA _____ DOD _____
 Regd. No. _____ JOPD: _____

Drug : _____
 Adverse Drug Reaction (ADR) : _____

Date of Onset : _____

Management of ADR : _____

OUTCOME OF ADR

Recovered without sequelae

Recovered with sequelae

Not yet recovered

Died due to adverse reaction

Died, drug may be contributory

Died, unrelated to drug

Unknown

Diagnosis: _____

Treatment

Drug(s)	Dose	Drug Administration	
		Began	Terminated

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRs)

The National Pharmacovigilance Centre, AIIMS, New Delhi invites reports of all suspected adverse reactions to drugs and other medicinal substances, including herbal, traditional or alternative remedies. The Centre particularly requests reports of:

- All suspected reactions to NEW DRUGS especially DRUGS OF CURRENT INTEREST and/or uncommon, severe and life threatening reactions to older drugs.
- All suspected drug interactions resulting in ADRs.
- Reactions to other drugs which are suspected of significantly affecting a patient's management including reactions suspected of causing:
 - rash
 - danger to life
 - needling in hospitalization
 - prolongation of hospitalization
 - absence from productive activity
 - increased investigational or treatment costs
 - birth defects

Send reports of adverse drug reactions (ADRs) to:
PROFESSOR S.K. GUPTA
 Chief, National Pharmacovigilance Centre,
 Department of Pharmacology,
 All India Institute of Medical Sciences,
 New Delhi-110029, India
 Tel. : 0091-11-2553030/2553032
 Fax : 0091-11-2553033/2553034
 Email : skgupta@aiims.ac.in

NOTES

REPORTED BY : _____
 Name _____
 Address _____
 Telephone No. _____
 Fax No. _____ E-mail _____

Information for patients

- Procure your medicines only from licensed retail pharmacies (chemist shops). Insist on obtaining a bill / cash memo or invoice for your medicines as this is your major guarantee against spurious / counterfeit medicines.
- Your medicines may expire well before their date of expiry if not stored properly.
- Store your medicines in a cool, dark & dry place. Kitchen or bathroom cabinets are not the appropriate storage places.
- The medicines prescribed for you are meant for you only. Do not give them to others even if their symptoms are similar.
- Taking alcohol with medicines can be harmful.

- For common ailments - consult your pharmacist. If the symptoms persist beyond 3 days refer your doctor.
- Do not self medicate, other than for minor ailments, or for more than 3 days.
- Do not discontinue taking your prescribed medicines until advised by your doctor. Take complete course of the prescribed medicines, particularly if they are antibiotics.
- You can import upto 100 doses of your medicines against your doctor's prescription. Contact CDSCO for further information in this regard.
- Keep all medicines out of the reach of children.

Imports of drugs for personal use

Small quantities of drugs, the imports of which is otherwise prohibited under Section 10 of the Drugs & Cosmetics Act, 1940, may be imported for personal use subject to the following conditions :

- (i) The drugs shall form part of a passenger's bona fide baggage and shall be the property of, and be intended for, the exclusive personal use of the passenger,
- (ii) The drugs shall be declared to the Customs authorities if they so direct
- (iii) The quantity of any single drug so imported shall not exceed one hundred average doses:

Provided that the licensing authority may in an exceptional case in any individual case sanction the import of a larger quantity:

Provided further that any drug, imported for personal use but not forming part of bona fide personal baggage, may be allowed to be imported subject to the following conditions, namely-

- (i) the licensing authority, on an application made to it in Form 12-A is satisfied that the drug is for bona fide personal use;
- (ii) the quantity to be imported is reasonable in the opinion of the licensing authority and is covered by prescription from a registered medical practitioner; and
- (iii) the licensing authority grants a permit in respect of the said drug in Form 12-B.

REPORT**1977-2002: 25 Years of Essential Medicines – A Commemorative Panel Discussion**

October 21, 2002, marked completion of 25 years of the global Essential Drugs Program that was launched in 1977 by the World Health Organization [WHO]. To commemorate this momentous occasion, CDMU, West Bengal, and Ramakrishna Mission Seva Pratishthan hospital, Calcutta, jointly organized a panel discussion at the hospital Seminar Hall. The program was in the afternoon and was attended by CDMU member partners, local pharmacists and hospital doctors.

After a brief but warm welcome address by Shri Sourendranath Sen, Honorary Secretary, CDMU, Dr. Avijit Hazra, Honorary Unit Coordinator, CDMU Documentation Centre, proceeded to set the background to the panel discussion through an audiovisual presentation. He sketched the worldwide campaign on essential drugs that began a quarter of a century ago as a way out from the therapeutic jungle that has grown through continued proliferation of drugs in the world pharmaceutical market. Using multimedia projection of powerpoint slides, some of which were obtained from WHO Department of Essential Drugs and Medicines Policy, he acquainted the audience with the meaning of essential drugs, the reasons why countries around the world have warmly embraced this concept as the foundation for national drug policies, the achievements globally over 25 years and the unfinished agenda of improving accessibility, tackling the spurious drugs menace, promoting rational drug use and counteracting the challenge of price barriers.

The panelists, drawn from different sectors of healthcare, and all experts in their own field, addressed a battery of questions. The key questions were:

To Dr. Santanu Kumar Tripathi, Professor of Pharmacology, Bankura Sammilani Medical College, Bankura.

- Leaving aside rhetoric and official records, does an essential drugs program really operate in India – public /

private / voluntary sectors. What has India achieved in this 25 years.

- With your long experience of undergraduate and postgraduate medical teaching, whether medical students, during their formative years, are exposed to the concept of essential drugs.
- What do you perceive are the major impediments to full implementation of this program in India.
- So far most essential drugs lists in the country restrict themselves to allopathic medicines. Can herbal formulations have a role in essential drugs programs.

To Dr. Debasish Ray, Assistant Drugs Controller, Central Drugs Standard Control Organization – East Zone, Government of India.

- What role does the Drug Control authority play to ensure the quality of drugs that are being marketed in India.
- What is the magnitude of the spurious drugs problem in India
- What can common people do to avoid fake drugs.
- What is the Government of India doing to popularize its Essential Drugs List and is there any official policy on rational drug use.
- How are marketing licenses given to some formulations that are perceived to be irrational.

To Dr. Dipankar Chakraborty, Principal, Institute of Pharmacy, Kalyani and Member, Pharmacy Council of India

- Do you feel that pharmacy students should be made aware of essential drugs concept and related matters such as rational drug use and prescription audits.
- How can practicing pharmacists strengthen this essential drugs movement in this country.
- Trivial medical problems can be taken care of by OTC products. Use of such products is routed through retailers. Is there any way to update their knowledge regarding the safe use of such products.

To Dr. Subhas Chandra Mandal, Inspector of Drugs, Directorate of Drug Control, Government of West Bengal and Secretary, Indian Pharmaceutical Association [IPA], West Bengal State Branch

- As representative of IPA, does this organization have any official stand as regards the essential drugs program.
- Proper selection, procurement and storage are integral to the success of any essential drugs programs. Are pharmacists in this country, by their training and the resources available to them, equipped to fulfill these norms.
- Do manufacturers in India take advantage of lax regulations and sell useless products to consumers in the name of Ayurvedic or herbal medicines.
- A formulary is an essential tool for rational drug use. Although we do have a national formulary [prepared by Indian Medical Association, Kerala State Branch], a formulary of the stature of British National Formulary does not exist in India. Is there any thinking, within the IPA, or otherwise to develop an up-to-date formulary of practical utility for Indian doctors and pharmacists.

To **Dr. Moloy Patra**, Secretary, Bengal State Branch, Indian Medical association [IMA]

- Do you feel that medical students should be made aware of essential drugs concept and related matters such as rational drug use and prescription audits.
- As representative of the largest umbrella body of doctors in India, i.e. the IMA, does this organization have any official stand as regards the essential drugs program.
- Many practitioners do not have access to medical updates and continuing medical education programs for various reasons. Given its nature and set-up, IMA perhaps is the only organization which can reach out to them at the moment. Is the IMA proactive in spreading the message of essential drugs and rational drug use.
- Can the IMA collaborate with other NGOs in spreading the message of essential drugs program and rational drug use.

At times, the tempo of the panel discussion heated up turning it almost into a debate and requiring concerted effort from the anchorperson to maintain the time schedule. The audience were infused with the spirit and a set of eager questions were put to the panelists once the structured discussion came to an end. Shortage of time played spoilsport but the discussion had served its purpose.

The 'take-home' message from the afternoon of deliberations were threefold:

1. The concept of essential medicines has global relevance for today's challenges and is particularly relevant for the conditions prevailing in India.



A section of the audience, in contemplative attention, at the Panel Discussion on '25 years of essential medicines' in Calcutta on October 21, 2002.

2. Essential drugs lists, formularies and standard treatment guidelines are the three pillars on which a program of rational drug use based on the essential drugs concept rests. Efforts to build up these pillars have been made in India but such efforts are still fragmentary and not strong enough to give the country's healthcare scenario a firm grounding in rational drug use. The efforts of many quarters – the government, non-governmental organizations, professional bodies of physicians and pharmacists – are, however, commendable and need to be encouraged. In particular, mutual cooperation of various agencies is the need of the hour.

3. Quality assurance and impartial drug information are also integral components of an essential drugs program. Recent developments in this field in India are heartening but a lot remains to be done.

Twenty five years is a long time for successful implementation of a program. Yet, the problem of providing equitable and affordable access to safe, effective and quality assured drugs to people around the world is so vast and so complex that the journey remains far from finished. In India, specially, the journey is a long and arduous one. It would require coordinated effort from all quarters, who have the benefit of the ailing fellow-beings at heart, to address the unfinished agenda and fulfil the dream of a healthy and just global society.



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Further information about the activities of CDMU may be found at <http://education.vsnl.com/cdmudocu/CDMUHome.htm>

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We wish our readers a happy, peaceful and prosperous New Year !

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