The ORION Medical Journal

IDEAL ANTIOXIDANT

Vol 4 September 1999

In Search of Ideal Antioxidant

Do Antioxidants Deserve a Closer Look?

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Contents

Cover Illustration: Combat of global population against various diseases most of them caused by "Free radicals".

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Editorial

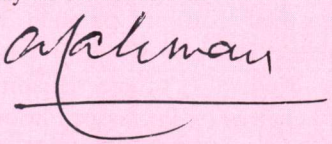
We are presenting our fourth issue of "The Orion" delighted by continueous encouragement and recognition from our dignified readers. It is our expectation that previous issue on ERID was subject of keen interest among valued doctors community and in reality it would be very much helpful in day to day practice.

In this issue we have dicided to focuss ***"Ideal Antioxidant"*** as main theme considering its worldwide research and observation among scientists.

Human being is very much worried about fatality of non curable diseases eg cancer, cardiovascular disease and progeria. Nutritional deficiency disorders in human are going to be increased day by day for adapting modern life, inclination to processed foods, explosive population growth coupled with poverty. From research and investigation it is now clear that vital oxygen is producing toxic products which are responsible for these non curable diseases and aging process. The discovery of antioxidant has created a new dimension in our medical practice and research. The role of antioxidants which are naturally existing in the body and adding to the body through foods becomes vital issue of research fellows of the world. Dream of human society is to remain active and sound even before last heart beat may be realised by supplimentation of ***Ideal Antioxidants*** which are more effective and harmless. Proper planning through international multidiciplinary collaborative effort is required to bridge the gap between the separate disciplines of free radical chemistry, cellular biology, and micronutrient nutrition in order to provide broader basis from which the suggested roles of pro and antioxidants in human diseases and aging will need to be studied.

We are confident that our attempt in highlighing this will alert all concerned. Suggestions or recommendations from our respected readers will be most welcome.

May all our readers be in the best of health and spirit.



Dr ATM Azizur Rahman
Chief Editor
and
Manager
Medical Services Department

MSD News

The Medical Service Department (MSD) of Orion Laboratories Ltd. spent a busy schedule in the second quarter of 1999. The members of MSD and Sales Department worked together with a view to serving the interest of the medical Professionals of the country.

CLINICAL MEETING

In Search of Ideal Antioxidant to Combat Cardiovascular Disease

Although the term **"antioxidant"** is quite familiar to us, we often confused to find out which antioxidant is best for us. Dr. Md. Mamtaz Hossain, Associate Professor and Head of the Department of Cardiology, Dhaka Medical College Hospital Carried out extensive study on antioxidants and free radicals. The result of his review revealed that although β-carotene is conventionally being used as an antioxidant, it has got no protective effect on cardiovascular disease and cancer mortality. On the contrary β-carotene demonstrated its detrimental effects on human beings in various established clinical trials. The combination of vitamin E and C may be considered to be the ideal antioxidant, as opined by Professor Md. Mamtaz Hossain. Based on this concept he, as keynote speaker delivered lectures on **"In Search of Ideal Antioxidant to Combat Cardiovascular Disease"** in some of the following venues:

Chittagong Medical College Hospital (CMCH), Chittagong on June 07, 1999 chaired by Professor R.K. Shaha (Head of the Department of Medicine, CMCH), Dinajpur Medical College Hospital, on June 17,1999 chaired by Professor Matlub Ahmed (Principal, Dinajpur Medical College), Rangpur Medical College Hospital on June 20, 1999 chaired by Professor M. A. Latif (Head of the Department of Medicine, RMCH), Sadar Hospital, Kurigrm on june 21, 1999 chaired by Dr. Mohaddes Hossain (Deputy Civil Surgeon, Kurigram), Dhaka Medical College Hospital (DMCH), Dhaka June 24, 1999 chaired by Professor Firdous Ara J. Janan (Head of the Department of Medicine, DMCH), Bangabandhu Sheik Mujib Medical University (BSMMU), Dhaka on June 30, 1999 chaired by professor KHMS Sirajul Haque (Professor and Chairman, Department of Cardiology, BSMMU), Sher-E-Bangla Medical College Hospital (SBMCH), Barisal on July 19,1999 Chaired by Professor M. A. Latif (Principal and Head of the Department of Medicine), Sadar Hospital. B. Baria on July 25,1999 chaired by Dr. Narayan Shaha, Senior Consultant (Pediatrics), Sir Salimullah Medical College Hospital (SSMCH), Dhaka on August 05, 1999 chaired by Professor M. A. Kashem Khandaker (Head of the Department of Medicine, SSMCH),

Importance of Zinc for Health

As a part of ongoing programmes of clinical meeting, MSD has further arranged number of Clinical Meeting on "Importance of Zinc for Health" in different venue to reiterate the significance of Zinc:

Sir Salimullah Medical College Hospital (SSMCH), Dhaka on April 12, 1999 chaired by Professor Rehana Begum (Head of the Department of Gynae and Obs. SSMCH), Sadar Hospital Gazipur on April 26, 1999, Chaired by Dr. Jalal Ahmed, Senior Consultant (Gynae & Obs.), Sher-E- Bangla Medical College Hospital, Barisal on May 17,1999 chaired by Professor Shah Alam (Head of the Department of Gynae and Obs. SBMCH), Tongi 50 beded Hospital on May 13, 1999, Chaired by Dr. Shamsun Nahar, (Senior Consultant, Gynae & Obs.), Sadar Hospital, Manikgonj on May 31,1999 chaired by Dr. Md. Rashiduzzaman (Civil Surgeon, Manikgonj), Bogra Medical College hospital, Bogra on May 31,1999 chaired by Professor Md. Mahfuzar Rahman, (Principal Cum Project Director, Bogra Medical College), Chittagong Medical College Hospital (CMCH), Chittagong, on June 08,1999 chaired by Professor Syeda Nurjahan Byuiyan (Principal and Head of the Department of Gynae and Obs. CMCH), Rangpur Medical College Hospital (RRMCH), Rangpur on june 15, 1999 chaired by Professor Azizul Islam, (Head of the Department of Gynae and Obs. RRMCH), Dinajpur Medical College Hospital on june 17, 1999 chaired by Professor Md. Nazrul Islam, (Head of the Department of Radiology, Dinajpur Medical College Hospital), Sadar Hospital Kurigram on june 21, 1999 chaired by Dr. Mohaddes Hossain (Deputy Civil Surgeon, Kurigram), Sadar Hospital, B. Baria on July 25, 1999 chaired by Dr. Narayan Shaha, (Senior Consultant, Pediatrics, Sadar Hospital, B. Baria).

LUNCHING OF NEW PRODUCTS

Now a days due to competitive life, there may be some unresolved conflicts which lead to a lot of anxiety and tension. To combat this situations ORION offers DETENS (Clobazam) - for those who respond to life's daily aggravations with unbearable anxiety or troublesome psychosomatic complaints, as DETENS (Clobazam)- alleviates acute and chronic anxiety states with the relief of associated psychic and psychosomatic symptoms.

In search of Ideal Antioxidants

Dr Khursheed Jahan, Dr ATM Azizur Rahman

Introduction :

In the modern world for the last few decades the subject "Antioxidant" is getting almost top priority in the research and clinical studies by the scientists and nutrition experts. Most of the non-curable chronic diseases e.g. cancer, cardiovascular disease, aging process till today have no remedy. Scientists are engaging themselves with their whole- hearted devotion and resources to overcome these burning issues of medical science.

Through various research the investigators observed some damaging agents in the normal human physiology as by products widely known as free radicals which are formed endogenously from normal metabolic process including cellular respiration, phagocytic activities of immune response, production of cytocrome P-450 enzymes and exogenously from exposure to radiation, environmental pollution, phenolic compound in food. Here comes question how to prevent attacks of free radicals in cells. To combat these attacks the theme of Antioxidant comes in the forefront in the field of biomedical research. Considering the impact, this field is going to be widely studied, discussed and focused through out the world by means of international seminars, symposium, journals, mass-media, internet communications and so on. From point of importance we want to reflect some current aspects of research findings of antioxidants which may be helpful to the doctors communtity of the country by updating the knowledge in this field to alleviate incurable sufferings of their patients.

Foods and Antioxidant :

Antioxidants are present in natural food staffs providing valuable degree of protection against oxidative attack in our body. Human being prefer processed food commodities than natural as society is adapting fast life to compete with the modernization. They have no enough time, enough man power, and no patience to prepare foods at home as it was to be. Subsequently due to consumption of commercial processed food human bodies deplete many important nutrients resulting in many nutrition deficiency disorders. Nutrition survey conducted in the country during last decades revealed the evidence of various nutritional deficiencies among the population. Hence protective mechanism against diseases by antioxidants becomes an important issue. The RDAs for different antioxidant nutrients suggested by various expert groups are just set for maintaining normal health but not for bodies under stressed conditions such as cancer, progeria, cardiovascular disease, any toxic condition and smoking. In these cases supplementation of antioxidant is essential.

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Manager MSD

How a life saving oxygen becomes toxic to our body

During normal metabolism of oxygen in the body most of it entering cell leaves as carbondioxide. 95% of remaining oxygen convert to water with addition of 4 electrons. Only 5% undergo addition of one electron-so become unimpared and result in formation of free radicals which are singlete oxygen, superoxide anion radical, hydroxyl radical. These compounds sometimes with some common metals like copper, iron and cobalt attack on important group of tissue constituents- notably lipids creating a number of deleterious effects, This is how vital oxygen becomes harmful to body. Chemical terms of free radicals and their actions are shown (table 1).

WHAT ARE THE FREE FADICALS BY CHEMICAL TERMS?

- ★ $O_2 \rightarrow$ SINGLET $O^{\bullet}$, SUPEROXIDE $O_2^{\bullet}$, $H_2O_2^{\bullet}$, $OH^{\bullet}$
- ★ $N \rightarrow NO^{\bullet}$
- ★ $C \rightarrow CCl_4^{\bullet}$

WHAT DOES IT DO?

LIPID PEROXIDATION
MODIFICATION OF PROTEIN
EFFECTS ON DNA > CELL INJURY OR DEATH / NEOPLASTIC TRANSFORMATION

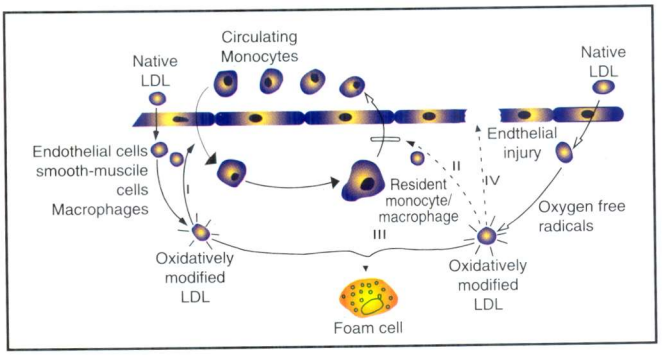
Fate of free radicals occurs in following ways (Table-2)

WHAT IS THE FATE OF FREE RADICALS?

- ☛ SPONTANEOUS DECAY
- ☛ ENZYMATIC DEGRADATION
  - ✦ SUPEROXIDE DISMUTASE (DOS)
  - ✦ CATALASE
  - ✦ GLUTATHIONE PEROXIDASE
- ☛ NON-ENZYMATIC DEGRADATION

  SERUM PROTEINS:
  - ✦ ALBUMIN
  - ✦ TRANSFERRIN

Some radicals react with non-radicals result in a free radical reaction chain and new radicals are formed. End products of these complex reactions are usually toxic to cellular components, cell membrane, and DNA and considered to be carcinogenic and with attack of lipoprotein development of atherosclerosis occurs. (Table-3)



Aging is a progressive accumulation of changes with time that, in human, occurs over decades. Concept has been modified that progressive free radical induced mitochondrial injury in post- mitotic cells is central to the aging process. Free radicals also are causing harmful effect through oxidative stress by certain toxins where (1) Toxin is its self a free radical (2) Toxin converted into free radical (3) Toxin is metabolized to generate free radical (4) Toxin antagonize antioxidant defenses. Besides these, free radicals have been implicated in over one hundred human diseases.

What is Antioxidant:

In deed it is paradox of nature that oxygen which is so essential to sustain aerobic life ultimately contribute to its damage. Fortunately a considerable amount of protection exist in the body in the form of antioxidant which combat free radicals. These are physiologically active intracellularly and extracellularly. By now antioxidants have become common discussion and recognition of this dilemma has generated a spate of antioxidant strategies.

Types of Antioxidants :

Broadly antioxidants are classified in five types namely Primary, Oxygen Scavengers, Secondary, Enzymatic and Chelating agents. At least 30 food spices and herbs have shown to poses antioxidant properties. The FAO/WHO[1] joint expert committee on food additive has given a list of 29 antioxidant compounds. Of these important ones are; Tocopherol, Ascorbic acid, β-carotene, Zinc, Selenium, and Glutathione. Among these Tocopherol, Vit C and β-carotene are much discussed with intensive studies. WHO also has given much importance on these three antioxidants.

Three Antioxidants in Brief :

1. Tocopherol (Vit E) :

From the outcome of recent studies on antioxidant Vit E possesses topmost position in respect of preventing formation of atherosclerosis by inhibiting lipid peroxidation, smooth muscle cell proliferation and platelet adhesion, It stops the degeneration of germinal epithelium, which reduce the danger of foetal death and also protect human from degenerative changes of dorsal column. Vit E is nontoxic and acts both inside and outside the cell. Life span of Vit E inside the cell is expected to be longer than that of other non-natural antioxidants. Vitamin E prevent the damage produced by *poly unsaturated fatty acid*[2] riched diet in liver and also play an important role in defense against radiation-induced free radical damage. It has synergistic action with Vit C that also regenerates Vit E inside the body forming complement antioxidant system. Vit E also has important role in enhancing immune system in body.

2. Ascorbic Acid (Vit C):

A reducing agent and water-soluble extracellular antioxidant. Functionally related to both Vit E and glutathion in lipid peroxidation and other oxidative conditions. It inhibits nitrosamine- induce carcinogenesis by directly reducing these compounds. Ascorbic acid has multiple effect on cellular redox system and functionally related to iron metabolism and iron- binding proteins. It enhances the release of transition metals from protein complex and reduces them to catalytic agent. Vit C can play vital role in collagen synthesis in wound healing, synthesis and maturation of RBC, triggering phagocytic response and synthesis of steroid hormone It is good scavenger of many free radicals and detoxifies inhaled oxidizing air pollutant (ozone, free radicals in smoking etc). It also prevents the damage caused by *poly unsaturated fatty acid* riched diet in the liver.

3. β-carotene :

Once thought to be beneficial for diminishing cancer mortality and cardiovascular disease but clinical studies in this respect revealed shocking results. β-carotene is shown not to be helpful at all, rather it is harmful. CARET, ATBC and Physician health study disclosed that β-carotene has no effect on cancer mortality rather it increase the risk of cancer mortality in smokers. It also evident from studies that β-carotene supplementation increase the risk of cardiovascular disease. In addition the highly accumulating effect of β-carotene resulting in hypervitaminosis-A increase retinol level in blood causing hypercholesteraemia; so limits the use of β- carotene indiscriminately.

In search of ideal Antioxidant:

Scientist and investigators are in search of ideal antioxidant to alleviate human sufferings. By this time two international congress on this subject were attended by eminent scientists, research fellows and investigators from all over the world and focussed on the out come of studies on antioxidant. These studies were clinical, nonclinical, observational, interventional, case control and follow up. Now we shall review some of these studies. In these studies showed inverse relation of consumption of Vit E with cardiovascular disease where as β-carotene showed adverse effects. In article "Antioxidant vitamins, cancer, and CVD" published in NEJM May 1996 vol 334 no 18 1189-1190, two reports should put to rest any remaining hopes that for adults β-carotene supplements may be an effective means of lower the risk of cancer and cardiovascular disease.

The physicians health study[3] followed more than 22000 male doctors treated with 50 mg of β-carotene for an average of 12 yrs and result unequivocally ruled out the possibilities that there is even slight reduction in the incidence of cancer and mortality from cardiovascular disease with such supplement.

After an average of four years of supplementation the combination of β-carotene and Vit A had no benefit and may have had adverse effect on the incidence of lung cancer and on the risk of death from lung cancer among smokers and workers exposed to asbestos[4].

Clinical trials with intervention

Randomised placebo based double blind case controlled study

CARET (β-Carotene & Retinol Efficacy Trial)[4]

"Effect of a combination of β-Carotene and Vitamin A on lung Cancer and Cardiovascular Disease"

- Place of Study: USA (multicentre)
- Total cases : 18,314 (smokers/ex-smokers/asbestos exposed)
- Supplemented 30mg β-carotene & 25,000 IU retinol (vit A) per day for average 4 years (stopped 21 months before planned due to negative findings; FU will continue for 5 yrs.)
- Results-Inverse association: Relative Risk of Death from:

Any cause	RR=1.17	95% CI (1.03-1.33)
Lung cancer	RR=1.46	95% CI (1.07-2.00)
Cardiovascular disease	RR=1.26	95% CI (0.99-1.61)

Combination of Vit E & C were found to inhibit glycation at physiological concentration and more effective than either vitamin, suggesting that synergistic antioxidant effect of these two nutrients may have contributed to the inhibition of glycation in diabetes mellitus[5].

Let us also review the following studies:

Antioxidant vitamins and Cardiovascular diseases : *Follow-up studies*[6]

"Vitamin e & C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly (EPESE)"

- Place of study : USA
- Total study population : 11,178 (67-105 yrs.)
- Follow up: 10 years (1984-1993)
- Result : Total death : 1490

Vit. E	All cause mortality	RR=0.66	95% CI (0.53-0.83)
	Coronary mortality	RR=0.53	95% CI (0.34-0.84)
Vit. E+C	All cause mortality	RR=0.58	95% CI (0.42-0.79)
	Coronary mortality	RR=0.53	95% CI (0.25-0.78)

Clinical trials with intervention

Randomised placebo based double blind case controlled study

Finnish ATBC (α-tocopherol, β-carotene) cancer prevention study[9]

"The Effect of Vitamin E and β-carotene on the Incidence of Lung Cancer and other Cancers in Male Smokers"

- Place of Study : Southwestern Finland
- Total cases : 29,133 (Male smokers), 50-69 years of age
- Supplemented 20mg b-carotene/50mg Vit. E (both alone & combined) per day for 5-8 years
- Results -

No change in incidence of lung cancers in Vit. E group but 18% (95% CI 3-36) higher incidence in β-carotene group. Total mortality 8% (95% CI1-16) higher in β-carotene group.

Clinical trials with intervention

Randomised placebo based double blind case controlled study

CHAOS[8]

"Randomised controlled trial of Vitamin E in patients with coronary disease : Cambridge Heart Antioxidant Study (CHAOS)"

- Place of Study : USA, 1982-1995
- Total cases : 2,002 (angiographically proven coronary atherosceloris present), av. 61.8 years of age
- Supplemented 400/800 IU Vit. E Per day of average 510 days
- Results -

Significantly reduced CV deaths & non-fatal MI (RR 0.53 95% CI 0.34-0.83). For non-fatal MI RR is 0.23 (95% CI 0.11-0.47)

Antioxidant vitamins and Cardiovascular diseases : *Follow-up studies*[7]

"Vitamin E consumption and the Risk of Coronary Heart Disease in Men"

- Place of study : USA
- Total study population : 39,910 (Male health professional free of coronary heart disease, diabetes & hypercholesterolaemia)
- Age : 40 to 75 yrs.
- Follo up for 4 years
- Inference : inverse association

Vitamin E	RR=0.64	95% CI (0.49-0.83)
β-carotene	RR=0.60	95% CI (0.38-0.94)

Conclusion :

From these studies and research we may come to a conclusion that world is now ***"In Search of Ideal Antioxidant"*** and planning further for more follow up studies to select ideal ones. For example human being are on aging process which leads to death-this is universal. But human desire to remain active and sound both physically and mentally before death. This demand may be fulfilled by using ideal antioxidant, which is the dream of the modern world.

To achieve this goal we must be cautious and rational about selection of an ideal antioxidant. β-carotene has several critical drawbacks and limitations. On the other hand Vit E tops the antioxidant chart in physiological and clinical point view. Vit C acts synergistically with Vit E and form complex antioxidant system. These are genuine reasons to consider the combination of Vit E and Vit C as ideal antioxidant to have maximum and optimal effect.

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Do Antioxidants deserve a closer look?

Perspective: Cardiovascular Disease

Dr KHMS Sirajul Haque

Introduction: Oxidation is a natural biological process that produces highly unstable and highly reactive atoms or molecules with unpaired electron in their outer orbit, known as free radicals.[1] They are produced by normal body functions like-cellular respiration, phagocytic activities of immune response as well as by external influences i.e. exposure to radiation (Ultra violet radiation, gamma radiation) and environmental agents.

Sources of Free Radicals

Exogenous :	**Endogenous :**
Ultraviolet rays,	Trauma, Surgery,
Smoking,	High fever,Infection,
Environmental toxic gases	Excessive exercise,

Free Radicals by Chemical name

Oxygen centered : Singlet oxygen ($O^{\bullet}$) ,
Superoxide $O_2^{\bullet}$, H_2O_2, $OH^{\bullet}$
Nitrogen centered : $NO_2^{\bullet}$
Carbon centered : $CCl^{\bullet}_4$

Fate of Free Radicals

- Spontaneous decay
- Enzymatic Degradation by
  - Superoxide dismutase
  - Catalase
  - Glutathione Peroxidase
- Non-Enzymatic degradation by serum proteins:
  - Albumin
  - Transferrin

Free radical damage- *the sequences:*
It is clear from various studies that free radicals cause continuous damage to our body, and complex defense system exist in the body to minimize it. Free radicals damage many cellular component, cell membrane, enzyme and DNA and other large molecules, mainly by three ways[2]:

1) Modification of Protein : At physiological pH, peroxinitrite produced by the reaction between two radicals damages protein directly, and decomposes it into toxic products.

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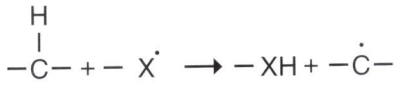
2) Attack of hydroxyl radical on guanine in DNA:

Guanine+$OH^{\bullet}$ → [Guanine-OH]$^{\cdot}$ (Oxidation) → 8-Hydroxyguanine radical

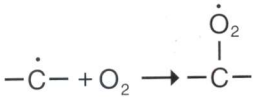
- 8-Hydroxyguanine: Mutagenic lesion
- Reduction → **Ring-opended guanine**: Halts DNA replication. Removal by DNA-repair enzymes may be hampered.

3) Lipid peroxidation : Reactive radical (such as $NO^{\bullet}_2$, $OH^{\cdot}$ $CCl_3O^{\bullet}_2$) abstracts atom of hydrogen from poly unsaturated fatty-acid side-chain in membrane or lipoprotein.

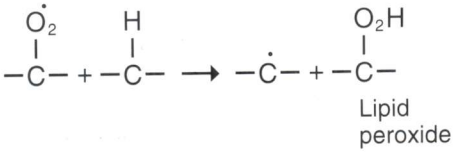
This leaves unpaired electron on carbon:



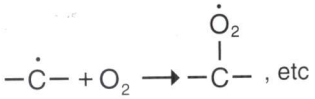
carbon radical reacts with oxygen :



Resulting peroxyl radical attacks adjacent fatty-acid side-chain to generate new carbon radical:



And chain reaction continues :



The interaction by one reactive free radical can oxidise multiple fatty-acid side-chains to lipid peroxides, damaging membrane proteins, making the membrane leaky, and eventually causing complete membrane breakdown.

ANTI OXIDANTS - The Scavenger of Free Radicals:

Antioxidants have become a familiar word and almost everyone is aware of their importance in protecting the body against damage by free radicals. A broad definition of an antioxidant is "any substance that, when present at low concentrations compared with those of an oxidizable substrate, significantly delays or inhibits oxidation of that substrate."[1]

NATURAL ANTIOXIDANT DEFENCE MECHANISMS- The inbuilt safeguard:

Antioxidant defences may be enzymatic and non enzymatic and have been evolved to protect against free radical damage both intracellularly and extracellularly.

Various enzymes inside the cell demonstrate their antioxidant property. Of them the important ones are : superoxide dismutase (SOD) & glutathione peroxidases (GSH) found in mitochondria and cystol, catalase-found in peroxismes in most tissues.[2]

Common antioxidants which are active outside the cell ,are plasma iron-transport protein transferrin, similar iron binding protein lactoferrin found in many body secretions (tear, nasal lining fluid etc.) haemopexin, hapatoglobin, ceruloplasmin.

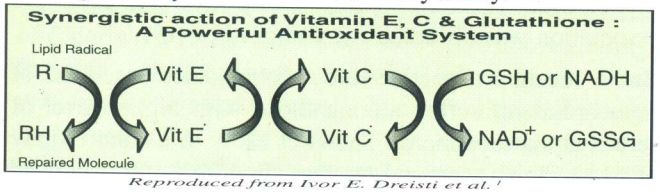
Some antioxidant defences are located and active both intracellularly and extracellularly. Of them α-tocopherol is the most potential one. Its site of action is membrane and lipoprotein. It blocks the chain reaction of lipid peroxidation by scavenging intermediate peroxyl radicals.[3]

MULTILAYERED DEFENCE SYSTEM AGAINST FREE RADICALS IN THE CELL

DEFENCE LINE	TYPE OF DEFENCE	MAIN LOCATION
1ST	CATALASE, Mn SOD	MT MATRIX
2ND	VIT E (MEMBRANE BOUND)	MT INNER MEMBRANE
3RD	Cu, Zn SOD	MT INNER MEMBRANE
4TH	GLUTATHIONE PEROXIDASE	CYTOPLASM
5TH	ASOCORBIC ACID, GLUTATHIONE, URIC ACID, CERULOPLASMIN	SERUM, TISSUES CYTOPLASM

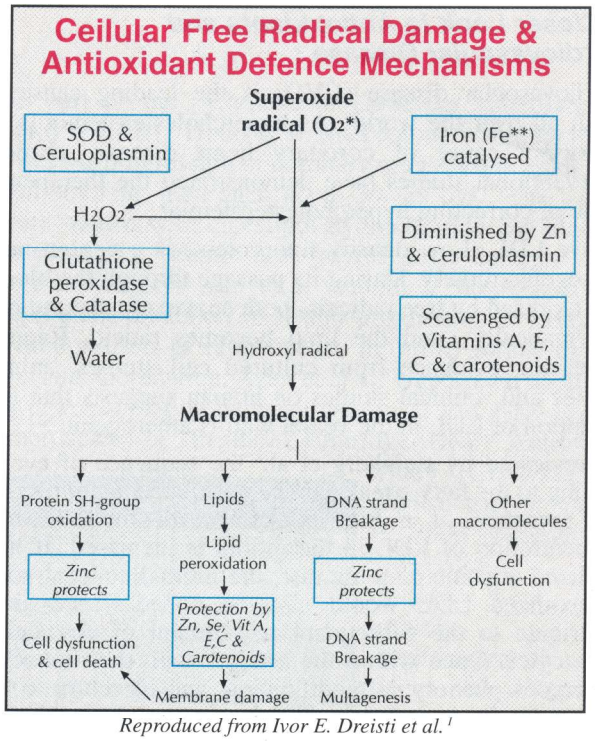
M T = Mitochondrion SOD = Superoxide dismutase

The tocopherol radical (T) is much less reactive in interacting with fatty-acid side-chains and can be converted back to α-tocopherol by vitamin C, SOD, GSH. α-tocopherol and ascorbate remove free radicals by reacting directly with them non-catalytically.



Reproduced from Ivor E. Dreisti et al.[1]

Some "free radical scavenges" come from the diet.[2] (table 1)



Reproduced from Ivor E. Dreisti et al.[1]

OXIDATVE STRESS-Initiation of disease process:

Unfortunately antioxidant defences mentioned earlier, are not completely efficient. Increased free-radical formation is likely to increase damage to our body.[2] The term **"Oxidative stress"** is often used to refer to this effect.[2]

If mild oxidative stress occurs, tissues often respond by making extra antioxidant defences. However, severe oxidative stress can cause cell injury and death, which can proceed as necrosis or apoptosis, and "antiapoptosis genes" in certain cells appear to encode free radical scavengers.[2]

This oxidative stress is imposed by the action of certain toxins through following mechanisms :

1) The toxin is itself a free radical, eg. nitrogen dioxide ($NO_2^{\bullet}$), the toxic gas in the polluted air. This compound is a good initiator of lipid peroxidation:

$$\text{Lipid} - H + NO_2^{\bullet} \rightarrow \text{lipid} + HNO_2$$

2) The toxin is metabolisd to a free-radical- eg, carbon tetrachloride is converted to a free radical by hepatic cytochrome P-450:

$$CCl_4 \xrightarrow{\text{P-450}} Cl^- + CCl_3^{\bullet}$$

This radical reacts with oxygen to give a peroxyl radical :

$$CCl_3^{\bullet} + O_2 \rightarrow CCl_3O_2^{\bullet}$$

3) The toxin is metabolished to generate oxygen free radical eg. paraquat in the lungs trigger the formation of superoxide radical.

4) The toxin depletes antioxidant defences, e.g. paracetamol when metabolised by liver cytochrome P-450 generates a product that reacts with and removes glutathione. Loss of glutathione cause secondary oxidative damage, which contributes to hepatic failure.

A Closer Look to Antioxidants and Cardiovascular Disease :

Cardiovascular disease (CVD) is the leading cause of death all over the world[5]. As hypercholesterolemia is an important cause of coronary heart disease, clinical interventional studies have demonstrated the therapeutic value of correcting hypercholesterolemia[6].

Native LDL (Low density lipoprotein) is a benign non-pathogenic moiety. During its passage through the blood, it is oxidised by free radicals- both enzymatically and non enzymatically and the lipid becomes rancid. Rapidly increasing evidence from cultured cell studies, animal studies and clinical studies on human suggests that this oxidation of LDL in the vessel wall is atherogenic.[6,12,13]

As reviewed by steinberg et al.[6] the sequence of events leading to the fatty streak can be postulated as follows. In the presence of a high plasma level of LDL, the concentration of LDL in the intima is increased. If it is oxidized at some ongoing rate, the intimal concentration of oxidized LDL would also be raised. It certainly contribute to the subsequent recruitment of circulating monocytes. Once within the arterial wall, the monocyte undergoes phenotypic modification, and its return to the plasma in its new guise of tissue macrophage is now inhibited by oxidized LDL. Since the macrophage can itself modify LDL oxidatively, the rate at which the oxidized LDL is produced may increase geometrically. As resident macrophages take up LDL much more rapidly in its oxidized form, they become foam cells.This foam cells lead to the development of atheromatous plaque. It is evident from the studies that antioxidant scavengers arrest this process by inhibiting LDL oxidation and thus reduce the risk of cardiovascular disease.

Vitamin C (Ascorbic acid): Although vitamin C is a strong antioxidant, the epidemiological evidence to support its individual role in lowering the risk of cardiovascular disease is inconsistent.[8] Results from cross cultural studies suggest a strong inverse correlation between plasma levels of vitamin C and cardiovascular mortality[7]. But results from observational studies do not support this suggestion. In a recent follow-up of 11,178 person from the Established Populations for Epidemiological Studies of Elderly (EPESE)[8], vitamin C supplementation alone had no effect on subsequent risk of coronary disease mortality. But in the same study it is shown that, combined supplementation of vitamin C with vitamin E significantly reduces the risk of coronary disease mortality, {Coronary mortality: RR =0.47 95% CI (0.25-0.87), All causes of of mortality RR = 0.58 95% CI(0.42-0.79)}.

To examine the direct role of vitamin C on atherogenesis, several studies have assessed atherosclerosis through carotid ultrasound and serial angiography. In a 2 year follow-up of 156 men with previous coronary artery bypass graft surgery, higher dietary and supplemental intake of vitamin C alone did not significantly alter the rate of coronary atherosclerosis as assessed by serial angiography[9].

Vitamin A (β-Carotene): The epidemiological evidence to support the cardioprotective effect of caroteonoids has grown over past several years, although the evidence supporting a specific benefit of β carotene is inconsistent. Moreover, a large clinical trial suggests an adverse effect of β-carotene supplementation[10].

Several observational studies have reported strong inverse association between diet high in β-carotene, and risk of coronary heart disease[11] . From these and other supporting evidence, several long term clinical trials were conducted to test the health benefit of pharmacological doses of β-carotene.

In the Alpha-Tocopherol Beta-Carotene Lung Cancer Prevention (ATBC) study[10], begun in Finland in 1985 among 29,133 male smokers aged 50 to 69. Men were enrolled in a randomized double-blind trial of β-carotene (20mg/day) or α-tocopherol (50mg/day). Men assigned to β-carotene had a higher mortality from ischemic heart disease than men taking placebo. From same study Rapola et al.[12] reported a significant positive association between β-carotene supplementation and increase in the risk of fatal ischemic heart disease (75% increase in the risk)[12]. Results from β-Carotene and Retinol Efficacy Trial (CARET)[13] also do not support a cardiovascular benefit of β-carotene supplementation. The CARET trial showed a non-significant 20% increase in the cardiovascular mortality with β-carotene supplementation.

Finally, in the Physicians Health Study[14], (the longest clinical trial of β-carotene to date), men assigned to 50mg β-carotene on alternate days did not experience a lower risk of cardiovascular disease as compared with men taking placebo.

Vitamin E (α-tocopherol) : Vitamin E is predominantly present in LDL and particularly effective in protecting it from oxidation and by this action, it reduces the risk of cardiovascular disease[15]. Laboratory data, recent animal and epidemiological evidence also support the hypothesis that vitamin E reduces the risk of cardiovascular disease. Gey et al.[16] found a remarkable inverse correlation between plasma vitamin E levels (adjusted for cholesterol) and the rates of coronary mortality. In the European Study on Antioxidants, Myocardial Infarction and Cancer of the Breast (EURAMIC)[17]- case control study of myocardial infarction, concentrations of alpha tocopherol in adipose tissue were assayed from 683 patients with acute myocardial infarction and 727 control subjects. No association was observed for vitamin E levels.

But a recent prospective study[18] found a decreased risk of myocardial infarction among those with higher level of serum alpha-tocopherol. Knekt et al. [19] in a cohort study of 5133 Finish men and women aged 30 to 69, followed them up for 14 years for occurrence of new fatal coronary heart disease.

Knekt and associates found that the rates of coronary heart disease were lowest among men and women who consumed the highest amounts of vitamin E.

In the Nurses' Health Study (NHS)[20] (the largest prospective cohort study to date) dietary data were collected in 1980 from 87,000 US female nurses, who were free from diagnosed cardiovascular disease and cancer at baseline. Participants were followed up for 8 years. From the study, Stampfer and his colleagues reported that women who used vitamin E supplementation for less than 2 years had little apparent benefit, but use for 2 years or longer was associated with a 41% reduction in risk of coronary heart disease. These finding persisted after adjustment for intake of carotene, vitamin C, and use of multivitamins.

In another prospective study of antioxidants and death from coronary heart disease, Kushi and associates[21] demonstrated that 10 IU of vitamin E daily reduced the risk of heart disease by as much as 62% in 34,468 disease-free post menopausal women. The result of this study support the use of vitamin E supplementation to prevent non-fatal myocardial infarction in patients with pre-existing cardiovascular disease and is consistent with two earlier prospective studies[22] of more than 87,000 women and nearly 40,000 men. These studies confirmed a reduction in the risk of cardiovascular disease among both men and women taking a minimum of 100 IU of supplemental vitamin E for at least 2 years.

The the Established Population for Epidemiologic Studies of Elderly (EPESE)[23] adds more support to above findings. In this observational study11,178 subjects were participated for up to 9 years. The actual dose of vitamin E is unknown(range: 50-100 IU) because of data collection methods, but the investigators reported that supplemental vitamin E (excluding multivitamins) reduced the relative risk of cardiovascular mortality by 47% and total mortality by 34%.

"FREE RADICAL SCAVENGERS" FROM THE DIE.T' (TABLE 1)

Constituent:	*Action:*	*Source*
Vitamin E(fat soluble), **known to be important**	General name for group of compounds, of which α-tocopherol is most important. Important in protection against cardiovascular disease because 1). It is predominantly carried in LDL and is particularly effective in protecting it from oxidation. 2) Vit E inhibits smooth muscle cell proliferation, and platelate adhesion thus prevents atherosclerosis. Vit E also protects human from degenerative changes of dorsal column & stops the degeneration of germinal epithelium- reduce the danger of foetal death.	1. Animal: Eggs, meats, liver, fish, chicken, milk. 2.Vegetable: Soyabean, seed oil, wheat etc.
Vitamin C (ascorbic acid) **Widely thought to be important**	Essential for several metabolic roles (e.g. in collagen synthesis and hormone production). Inhibits nitrosamine carcinogenesis by direct reduction of these compounds. Probably assists α-tocopherol in inhibition of lipid peroxidation by recycling the tocopherol radical : T + ascorbate > TH + ascorbate. Good scavenger of many free radicals and may help to detoxify inhaled oxidising air pollutants (ozone NO2, free radicals in cigarette smoke) in the respiratory tract. In animal high concentration ascorbate partly compansate for low levels of GSH.	1.Vegetable: Amlaki, orange,lemon, guava, pineapple, etc. Fresh vegetables eg. cabbage, cauliflower, green peppers, etc. 2.Animal: Generally poor but milk contains small amount.
β-carotene, other carotenodis, related plant pigments. **Probably Important, but not necessarily as antioxidants**	Once thought to be helpful for diminishing cancer mortality & cardiovascular disease, but recent studies (CARET, ATBC & Physician's health study) disclosed that b-carotene has no effect on cancer mortality, rather it increases the risk of cancer mortality (CARET study). It is also evident from the studies that β-carotene supplementation increases the risk of cardiovascular disease, specially in smokers[3]. Moreover accumulating effect of b-carotene, results in hypervitaminosis A.	1. Animal source: Cod liver oil, liver, egg yolk, milk, milk products- butter, cream. 2.Vegetable: Green leafy vegetables- carrots, papyes, yellow mangos & bananas.

As part of the Cholesterol Lowering Atherosclerosis Study (CLAS)[24] Hodis et al. used coronary angiography to asses the progression of coronary artery lesion among 162 non smoking men aged 40 to 59 yrs old. The patients were treated with cloestipol hydrochloride and niacin or supplemental vitamin E at varying doses during a 2-year period. Subjects who took vitamin E supplements had significant reduction in lesion progression as compared with non-users of supplements. In further follow-up from the same population, Azen et at al.[25] reported a significant inverse association between vitamin E and early invasive atherosclerosis. In the Cambridge Heart Antioxidant Study (CHAOS)[26] the clinical trial of vitamin E, 2000 subjects with preexisting heart disease were given vitamin E supplementation of 400 IU or 800 IU over 18 months. Results showed that vitamin E supplementation reduced the risk of non-fatal myocardial infarction by 77%.

The ATBC study[27] found that there was no discernible effect of vitamin E on fatal ischemic heart disease, that there was a beneficial effect of vitamin E on non-fatal myocardial infarction (a risk reduction of 38%).

It is important to note that the result of CHAOS and ATBC studies are entirely consistent with those observational studies NHS[20] & HPFS[11].

Conclusion: In this plethora of the above clinical informations, conclusions on antioxidant vitamin supplementation can be drawn after getting the results of ongoing clinical trials of primary and secondary prevention, namely the Women's Health study[28], a continuation of physician's Health study and Heart Outcomes Prevention Evaluation (HOPE)[29] study. Meanwhile there is sufficient reason for physicians, to believe that- vitamin E & C supplementation seems to be cardioprotective but further study are required to conclude on the role of β-carotene in prevention of cardiovascular disease.

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Spring Planting

Prematurity and Low Birth Weight : An Overview

Professor M. R. Khan

INTRODUCTION

Birth weight of an infant is highly sensitive in two important aspects: *firstly*, it is strongly conditioned by the health and nutritional status of the mother; *secondly,* it is the single most determinant of the chances of newborn to survive and experience healthy growth and development.1

Birth weight less than 2500g is termed as Low Birth Weight (LBW).[2] LBW is a major public health problem in developing countries including Bangladesh. WHO estimates that 17% of all births in the world are of LBW.[4] Incidence of LBW in Bangladesh is 38%[3] - 50%[4]. In India and Srilanka it is 33% and 25% respectively. In developed countries like USA, UK and Japan incidence of LBW is only 7%.[4] (75% of LBW are IUGR-WHO, 1980)

LBW is an important risk factor associated with a high perinatal and infant mortality. Neonatal mortality (54/1000 livebirths[5]) contributes some two third of the (IMR 81/1000 livebirths[4]) and early neonatal death (death within 1st week of life) is 33% of IMR in Bangladesh. The majority of these deaths are a consequence of LBW. The relative risk of morbidity among LBW infants is high.

Premature newborns are also at increased risk of morbidity and mortality. Particularly of the LBW babies, those who are preterm and LBW, means AGA, they are more vulnerable to have morbidity & increased risk of death.

OTHER SURROGATES/ALTERNATIVE TO BIRTH WEIGHT[6]

- Chest Circumference at Birth (CCB)
- Head Circumference
- Foot length
- Abdominal Circumference

CCB is the best surrogate

CCB cut off level (WHO) = 300 mm (30 cm)

= corresponds to birth wt <2500g

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In Matlab study (ICDDR,B, 1994)

Mean CCB = 306 mm

= Corresponds to birth weight 2620g

* The mean CCB of 25 newborn died within 4 months of life was 274 mm (27.4cm) compared to those who survived 4 months was 307mm (30.7cm)
* The relative risk of dying within 4 months of life between CCB<30.6 cm and CCB>30.6cm is 7.8
* The relative risk of dying within 1 month of life between CCB<30.6 cm and > 30.6 cm is 43.
* 31 % of nenoates had CCB < 30 cm (LBW).
* 50 of mothers refused to weight their babies. (therefore, measuring chest circumference is more feasible in the community)

ETIOLOGICAL FACTORS

LBW is a result of[2]

* Prematurity (a gestational age below 37 weeks) and / or
* Intra-uterine growth retardation (below the 10th percentile of the reference standard for birth weight and gestational age)

The important contributing factors are[2]

- Low maternal calorie intake
- Inadequate weight gain during pregnancy
- Low prepregnancy wight
- Maternal diseases like Nutritional Anemia, Hemorrhage, Infections (Including reproductive tracts), Toxemia of pregnancy, Diabetes etc.
- Short stature
- Early child birth (during teen age-before 16 years)
- Over work during pregnancy (inadequate rest)
- Narrow birth spacing
- Fetal causes like multiple pregnancy, malformations
- Tobacco intake in any form including passive smoking
- Malaria

Problems of LBW

- High neonatal mortality
- Morbidity
  - Increased susceptibility to infections
  - Hypothermia
  - Hypo or Hyperglycemia
  - Hyperbilirubinaemia
  - Early anemia of infancy
  - Metabolic bone diseases
  - Neurological deficit (CP) and others

Guidelines for the management of LBW

- *Warming*
- *Early colostrum feeding*
- *Protection against infection*
- *Early referral to higher centres (when necessary)*

Prevention

a) Proper and adequate antenatal care

- Regular check of BP
- Urine examination (for sugar, albumin and infections)
- Edema
- Weight gain during pregnancy in our country <5 Kg and >9 Kg in developed countries)
- Correction of anemia (iron-folic acid supplementation)
- Food supplementation with adequate caloric and Protein

b) Upliftment of Social condition

General education and awareness on reproductivity health emphasizing nutrition which will prevent the risk and contributing factors for LBW-eg. early marriage, frequent child birth and awareness in mothers' nutrition.

c) Upliftment of economic condition of mothers

Mothers should be empowered to gain economic solvency.

Different NGOs, and GOs are keen & already involved in this field.

CONCLUSION

It is a gigantic task, steps are not very difficult. Obstetricians, Pediatricians and General Practitioners, NGOs and GOs and mass media have got role to play to reduce LBW and child health.

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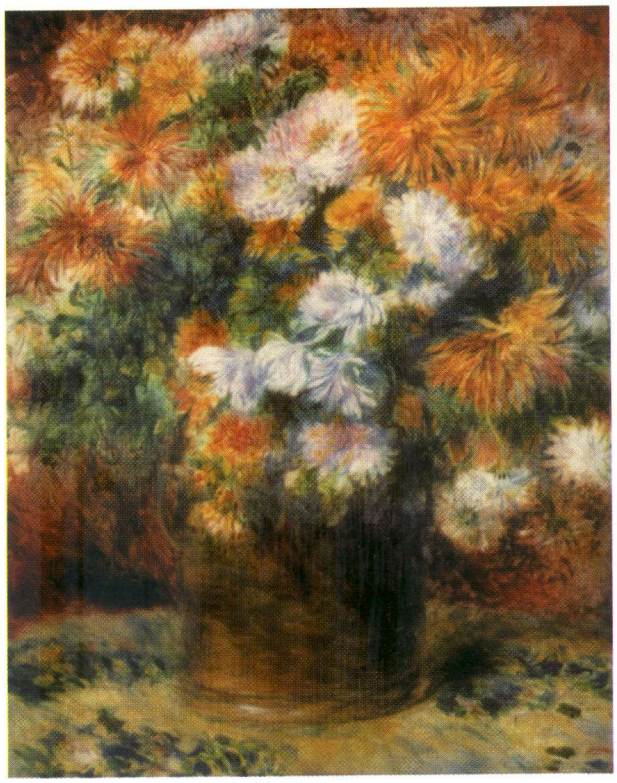

Pierre Auguste Renoir.
Chrysanthemums, *1881/82,*
French.

Urinary Tract Infections in Pregnancy

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Urinary tract infections (UTI) are remarkably common in women. Some 20% Women in the age range 20-65 years suffer at least one attack per year, 50% develop a UTI within their lifetime[1]. Not surprisingly infections of the urinary tract are the most common bacterial infections encountered during pregnancy. These can be both asymptomatic and symptomatic affecting both upper and lower urinary tracts.

Aetiology:

The major reason why urinary tract infections are more common in women than men is anatomic. The female urethra is relatively short, averaging 3- 4 cm in length, and thus act as barrier to invading pathogens. Moreover, it is in relatively close proximity to both the vagina and the rectum and therefore may be more readily colonized by enteric organisms.However, the mechanisms responsible for the increased susceptibility to symptomatic UTI in pregnancy continue to be debated. The Enterobacteriaceae account for approximately 85-95% of infections.

Prevalence of asymptomatic bacteriuria in nonpregnant women rises with age at the rate of about 1% for each decade of life from at least age 5 onward. The prevalence of bacteriuria not only increases with age but also with sexual activity, parity, and sickle cell trait.

The higher prevalence rates (11%) have been seen in socially indigent multiparas, as compared with about 2% in pregnant patients in private practice[2]. Multiparity is also associated with increased bacteriuria in pregnancy[3]. Sickle cell triat has been cited as another association with bacteriuria, reflecting renal parenchymal damage[4,5].

Commonly isolated pathogens in women with urinary tract infections:

The *Escherichia coli* account for approximately 85-95% of infections. Followed by *klebsiella Enterobacter.*[6]
Eschericha coli
Khebsiella- Enterobacter
Streptococcus
Staphylococcus
Proteus
Pseudomonas

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More recent studies have shown that by culturing for ureaplasmas and other fastidious organisms, the prevalence of bacteriuria may be as high as 25%. However, it is unclear whether *Ureaplasma urealyticum* and *Gardnerella vaginalis* found in the bladder urine of some pregnant women, play a significant pathogenic role.[7]

Changes of Genitourinary system during pregnancy :

The changes that take place in the urinary tract during pregnancy may simply permit urinary colonization established prior to pregnancy to lead to symptomatic infection. Pregnancy does not seem to enhance virulence factors, but urinary stasis and diminished ureteral tone and peristalsis caused by ureteral compression of the enlarging uterus and to a lesser extent by the smooth muscle relaxant effects of progesterone predispose to symptomatic urinary infections.[8] Because relatively few women become bacteriuric during the course of pregnancy and because there is no evidence to suggest that bacteriuria present early in pregnancy has been acquired at the time of or since conception, it seems likely that the frequency of symptomatic UTI during pregnancy reflects asymptomatic bacteriuria acquired periodically by certain woman very early in life or later.[9]

Though some authors (Patterson TF et al.) believe that profound physiologic changes affecting the entire urinary tract- occur during pregnancy may have a significant impact on the natural history of UTI during gestation.[10]

Dilatation of the upper collecting system occurs in most normal pregnancies and extends down to the level of the pelvic brim. These changes are more pronounced on the right than the left, largely owing to the sharp angle of the right ureter follows on its drop into the pelvic cavity. Ureteral peristalsis is reduced after the second month of gestation, with long periods of complete atony seen in the seventh and eighth months of pregnancy, likely a result of hormonal change.[11] Dilated ureters can hold up to 200 ml of urine.[12]

The bladder, like the ureters, undergoes a progressive decrease in tone and a subsequent increase in capacity . Later in pregnancy, the bladder may contain double its normal volume without discomfort.

Some other studies have suggested that hormonal rather than mechanical changes seen during pregnancy may be

the primary factors involved in the aetiology of hydroureter.[13]

These changes vary from patient to patient and are more likely to occur during first pregnancies or in women who have had their pregnancies in rapid succession. The urinary tract tends to revert to normal by the second month of the puerperium.

Asymptomatic infections (asymptomatic bacteriuria) :

The reported prevalence of asymptomatic bacteriuria during pregnancy varies from 2% to 12% depending on parity, race, and socio-economic status. The highest incidence has been reported in black multiparas with sickle cell trait and the lowest incidence in affluent white women of low parity. Asymptomatic bacteruria is twice as common in pregnant women with sickle cell trait and 3 times as common in pregnant woman with diabetes as in normal women.

A woman is considered to be suffering from asymptomatic bacteriuria when there is presence of significant bacteria (by definition, $\geq 10^5$ of a single uropathogen per mL of urine collected via clean-voided midstream sampling) without associated symptoms such as dysuria, frequency or suprapubic discomfort. Counts of less than 10^5/ mL or specimens yielding two or more organisms probably represent contamination and not infection.[14] To avoid confusion of contamination it is better to carry out the test in two consecutive specimens.

Though it is not causing any apparent problem to the mother but up to 25-30% of women will develop acute pyelonephritis and according to some studies this may be as high as 50% if remain untreated and even treated the affected population will be near10%.

Keeping the delayed complications in mind, it is wise to treat these cases with antibiotics whenever they are detected. Different antibiotics with different durations have been tried so far. The duration of therapy for bacteriuria of pregnancy has received much attention. Early studies used continuous therapy until term because of the concern about treatment failures following short-course therapy.

More recent studies have evaluated single-does therapy for bacteriuria in pregnant women. It has been suggested that pregnant women, like nonpregnant women with renal infection, were more difficult to treat and had higher failure rates with single-does therapy. Since then more trials have shown that single-dose therapy effectively eradicates bacteriuria in pregnancy. But the important issue is not the length of therapy chosen but that appropriate follow-up is obtained to document the elimination of bacteriuria

The main problem of treating these cases is that while selecting the drug we have to take both the mother and the fetus in consideration. The effect of Ampicillin, Amoxicillin, Cephalosporin, have so far been widely studied and all of them gave good result.[15] Ronald et al. used nitrofurantoin, also got as good result as others.[16] But the use of this drug should be restricted to early pregnancy as it may induce haemolytic anaemia. Pedler et al. in 1985 showed use of augmentin gave significantly good result.[17] In 1983 Campbell et al. found that single does therapy has lower initial cure rate.

An affective drug for UTI is trimethoprim-sulfamethxazole. It is necessary to avoid sulfa drugs during pregnancy due to increased occurance of neonatal hyperbilirubinaemia.

Symptomatic UTI:

Symptomatic infection of the lower urinary tract (acute cystitis) is usually manifested by dysuria, frequency, urgency along with positive urine culture. In the absence of upper tract involvement patients do not have systemic symptoms like fever, nausea, vomiting. Acute pyelonephritis is usually associated with loin pain. Presence of only increased frequency of micturition or nocturia is usually not the symptom of UTI during pregnancy as it can be a normal physiological adaptation of pregnancy.

Urine analysis of these patients reveal pus cells, white cell casts, bacteriuria. Presence of haematuria indicates urinary calculi. The diagnosis needs to be confirmed by urine culture.

Beside the usual complications of pyelonephritis like septicaemia, endotoxic shock, acute renal failure, pulmonary dysfunction-the other important concern for obstetricians is the effect of UTI on the foetus which includes IUGR and pre-maturity.

Any pregnant mother who are suspected acute pyelonephritis should be handled intensively and hospital admission is indicated. Antibiotic therapy needs to be started from very begin even before getting the urine culture and sensitivity report. This cases should be treated with intravenous antibiotics initially and after the systemic manifestation (fever, vomiting) improves, oral regimen can be started. Penicillin and cephalosporin is the drug of choice but incase of penicillin resistant cases (no improvement within 48-72 hours) aminoglycoside like gentamicin can be helpful.

28% of women with pyelonephritis can develop recurrent bacteriuria and 10% recurrent acute pyelonephritis during the same pregnancy.[18] In these cases long term prophylactic treatment with Nitrofurantoin, 100 mg every night is advocated by some authors although the efficacy of such therapy is questionable.

Conclusion:

In all patients with bacteriuria of pregnancy should be treated and followed up cultures are taken to document response. Therapy should be as brief and non-toxic as possible to both mothers and fetuses. All cases of persistent asymptomatic bacteriuria throughout pregnancy or even a single attack of acute pyelonephritis need through post partum investigations.

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THE NOBEL CHRONICLES

As there was no consensus, the Nobel Prize in Physiology or Medicine was not awarded in 1925. In 1926 the Prize was awarded to Johannes Fibiger for the discovery of *Spiroptera carcinoma.*

1926:Johannes Andreas Grib Fibiger (1867-1928)

Fibiger was born in Silkeborg Denmark. He studied, bacteriology under Robert koch and, in 1900 became Director at Copenhagen's Institute of Pathological Anatomy.

In 1907, Fibiger discovered papillomatous stomach tumours in laboratory mice. Within the tumours he found peculiar nematodes, which he later named *Spiroptera neoplastica*. Believing nematodes to be the cancer- causing agents, Fibiger pursued his studied, but failed to find any parasite in nearly 1000 mice tested. Later, in a Copenhagen sugar factory infested with mice and cockroaches, he found the same nematodes in 75% of mice, 20% of which also had tumours.

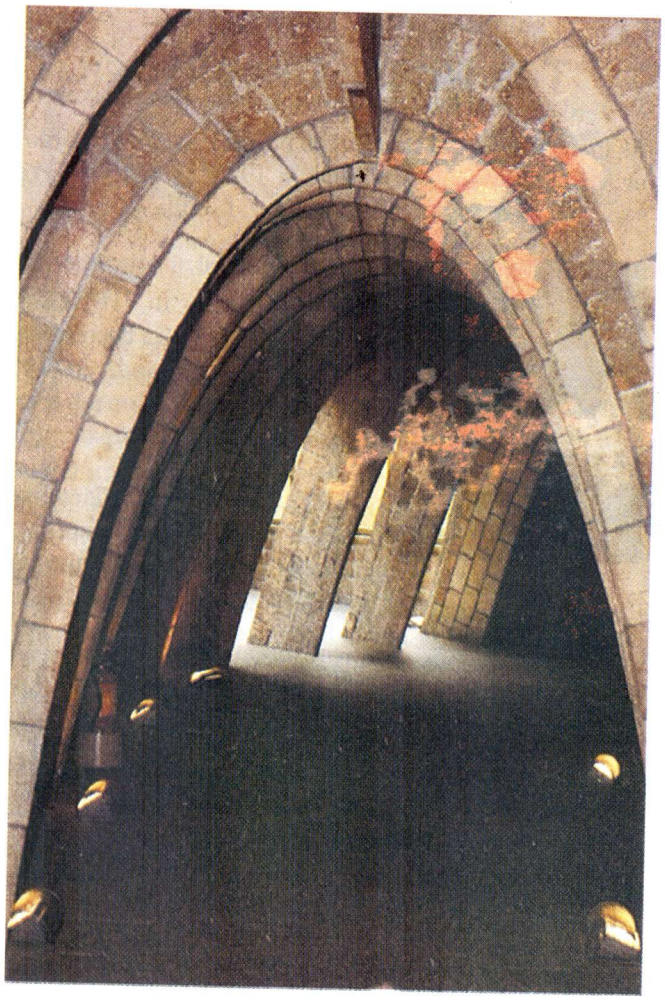
In 1913, he proposed that cockroaches become infested by eating mice excreta containing parasitic eggs, and that mice are re-infected by eating the larvae-Iaden cockroaches; irritation or chemicals from the nematodes caused cancers.

Some experts agreed, but most were skeptical of Fibiger's hypothesis. They could not replicate his findings and concluded that parasites were incidental finding. Subsequently, diets deficient in vitamin. A were also shown to cause mice stomach cancers, and Fibiger's theory was forgotten. Because of the ``error'' of honouring fibiger, the Nobel Foundation avoided recognising subsequent cancer research for 40 Years.

There is little dispute today about infections causing malignant diseases; the discovery of the association of *Helicobacter pylori* with stomach cancer has enhanced interest in Fibiger. Fibiger was an eminent scientist deserving our recognition. William Campbell, a parasitologist, notes: ``Fibiger may have been barking up the wrong tree, but he was still a Grreat Dane'',

THE LANCET. Vol. 352. NOVEMBER 14, 1998.

Medi Image



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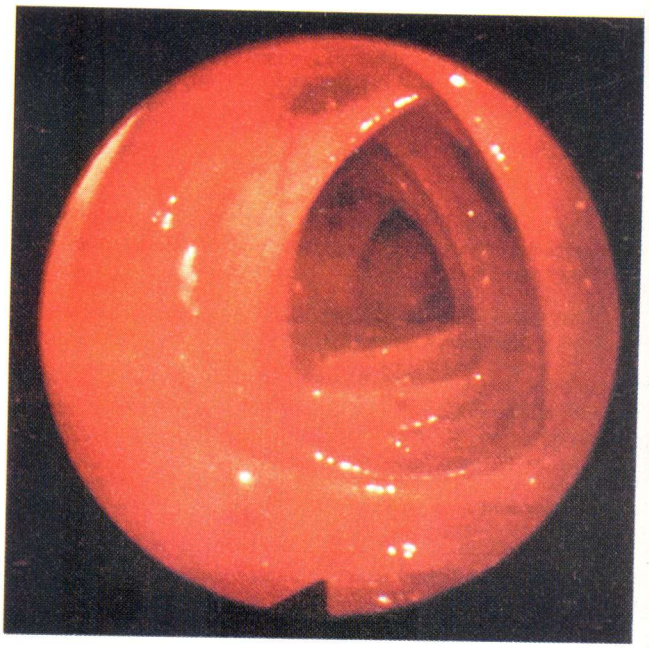

B

THE GAUDI-COLON CONNECTION

Antonio Gaudi, a world-famous architect, was a leader of the artistic movement known as modernism, which is based on the use of natural forms. On 1906, he built La Pedrera, one of his most prominent buildings in Barcelona, Spain. The arcades of the upper floor (Panel (A), recently restored and opened to the public, are very similar in form to the haustrations of the transverse colon (Panel B) seen on colonoscopy in our daily practice. Colonoscopy was introduced in the 1960s. Was Gaudi a visionary who anticipated, 60 years earlier, the images now shown by modern endoscopy?

MediQuiz - 3 Answers

1.	A,D	8.	E	15.	B,C
2.	D,E	9.	A,B,C,D,E	16.	A,C,D,E
3.	A,C	10.	D,E	17.	C,E
4.	None	11.	B,C,E	18.	A
5.	C,D	12.	B	19.	A,B,C
6.	A,C,D,E	13.	C,E	20.	A,C.D,E
7.	A,B,D	14.	A,C,E		

Nausea And Vomiting of Pregnancy

Dr. Suraiya Begum, Professor Syed Ershad Ali

Introduction

This is one of the most common of all the tribulations of the first trimester. It is usually most severe in the morning that is why morning sickness became a commonly used but essentially descriptive term. The American nomenclature of nausea and vomiting of pregnancy (NVP) is bland but holds serval advantages. It is unbiased towards any putative causes, it allows for a spectrum of severity and it differentiates between the subjective symptom of nausea and the objective sign of vomiting.

Types : Nausea and vomiting of pregnancy may be-

Mild : Nausea only.

Moderate : Nausea and vomiting

Severe : Vomiting leading to dehydration, weight loss and electrolyte disturbance.

Mild to moderate NVP are equivalent to what used to be called physiological vomiting. Severe NVP means hyperemesis gravidarum.

Aetiology

Mild to moderate NVP complicates 70% of all pregnancies- typically starting by four to six weeks of gestation, peaking in incidence and severity by eight to twelve weeks and resolving spontaneously by the 20th week. It is the commonest complaint of the first five months of any pregnancy and is probably due to rapidly rising oestrogen levels characteristic of the first trimester although increased progesterone and reduced motilin have also been incriminated. When occurring later in pregnancy it must likely represents a mechanical action by the enlarging uterine fundus on the diaphragm and cardiac and pyloric sphincters. Mild and moderate NVP are therefore physiologically and statistically normal.

Severe NVP

Hyperemeisis gravidarum. There is more controversy over severe NVP. Important causes are summarised as follows:

1) Human chronic gonadotrophin hormone is often quoted as the causative agent because women with multiple pregnancies or Hydatidiform mole (i.e. conditions associated with abnormally high HCG levels) are more likely than other pregnant women to have severe NVP.

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2) Reflex oesophagitis : Recent studies suggest that reflex oesophagitis in association with gastric dysrythmia is causative-the trigget to vomiting being changes in gastric PH (Devil-1991)

3) Other incidental cause :
1) Gynaecological :
Twisted ovarian cyst.
Red degeneration of fibroid

Right sided Positioning of the corpus luteum (suggested to act by exposing the hepatic portal system to high concentration of oestrogen).

2) Medical
Peptic ulcer
Gastro enteritis
Pyelitis
Uraemia
Diabetes

3) Surgical
Intestinal obstruction
Acute appendicitis
Acute cholecystitis
Intracranial lesion

4) Endocrine

Adrenal dysfunction (Jarvinen et al. 1962)

Thyroid disorders (Beeks and Burrow 1991)

5) Psychogenic basis is explained as it is more common to unmarried pregnancies and unwanted pregnancies.

6) Social

It is known that social factors are associated with severe NVP. Surveys have found heigh proportions of women with severe NVP living in overcrowded or unfamiliar circumstances with women from abroad more likely to suffer NVP than indigenous population (Fair weather 1966).

Impact of severe NVP on Pregnancy

Relatively few studies have attempted to relate NVP to other outcomes. Chain and Lao (1988) found an association between severe NVP and intrauterine growth retardation. Godsey and Newman (1991 found that women repeatedly admitted with recurrent hyperemesis failed to gain weight satisfactorily during their pregnancies and produced low birth weight babies significantly more offer than controls. Fair weather (1956) found a 40% risk of previous pregnancy loss (either by miscarriage or prenatal mortality) in women with severe NVP.

On the other hand in a prospective study of more than 16000 women there was no difference in the incidence of congenital defects between those who had vomited in pregnancy and those who had not (klebanoff and Mills 1986).

More over moderate NVP has been found to lower the risk of complete miscarriage if it occurs in the context of a Threatened miscarriage (Wiegel and Wiegel 1989)

This protective effect is absent in mothers not suffering from NVP which may indicate lower levels of oestrogens. Severe NVP has no apparent effect on the outcome of threatened miscarriage but curiously seems to protect against postnatal depression, a condition which is over represented in mothers who were NVP free during their pregnancy. Those with mild or moderate types occupy an intermediate position.

Pathology and Biochemical changes

There are no specific morbid anatomical findings and the changes described by Sheehan (1939) in the liver, heart, kidneys and central nervous system are common to all cases of severe malnutrition what ever the cause. The lesions in the brain stem resembling Wericke's encephalopathy are probably due to vitamin B deficiency.

The biochemical changes which occur can also be attributed to chronic starvation and are not specific for hyperemesis. There is a loss of water and salt with consequent haemoconcentration and reduction of urinary chlorides. Extracellular fluid is diminished and plasma, sodium and chloride are reduced. Ketosis occurs and the blood urea is elevated as a result of the disturbance in nitrogen metabolism. Potassium deficiency soon follows, as potassium is not stored by the normal adult and rapid loss occurs in the vomit and in the increased renal excretion.

This hypokalaemia may cause further vomiting which, together with liver damage, sets up a vicious circle difficult or impossible to break.

Treatment

Principal

1. Restoration of normal water electrolyte balance.
2. Provision of adequate nutrition.
3. Stoppage of vomiting.

Mild cases of NVP

The treatment of NVP has traditionally been supportive with dietary advice (dry toast before rising and no fatty foods) being supplemented by antacids. The most widely used prescription medication until ten years ago was debendox, consisting of a combination of dicyclomine (a synthetic antimuscarinic agent), doxylamine (a sympathomimetic present in many common cold remedies) and pyridoxine. Debendox was withdrawn in 1983 following unsubstantiated claims of teratogenicty.

By this time the infamous thalidomide disaster had already occurred and preserving for NVP dwindled in the 1980s. Despite this, a number of trials have found various antihistamines to be superior to placebo. They are generally considered to be safe during pregnancy although there have been no major epidemiological studies to look for teratogenic effects (Enkin et al. 1989). Neither the efficacy nor the safety of phenothiazines or metoclopramide have been established despite continued common usage.

Severe cases of NVP

Assuming infective commonly (urinary tract), metabolic (e.g. diabetes), intraabdominal (ovarian cyst or even appendicitis) and intracranial causes have been ruled out, admission for rehydration and correction of electrolytes is indicated for resistant, severe NVP.

Role of Psychotherapy

The possibility of a psychological component to the aetiology of severe NVP was first raised by Lucile Dookley (1920) in her psychoanalytic of charlotte Bronte's personality, in which she stated "pernicious vomiting always has psychogenic features" assessing Bronte as having been "fearful, conflicted and reluctant to accept her future marriage and child bearing. While accepting organic factors in the illness Dookley assumed "with certainty that her condition was aggravated by psychogenic reactions derived, probably, from the fear and reluctance she felt at this new facing life". Rhodes (1972)reattributed Bronte's death to severe NVP and stated that "hyperemesis gravidarum only seems to be excessive in excessive in those who display neuroticism".

The case study of an elderly primipara with "severe hyperemesis" (Hurst 1943) is the first in which such theory was put into practice. Sir Arthur Hurst's patient was treated with "good common sense medicine and a great deal of psychotherapy and reassurance". Following Hurst's work, hyperemesis generally came to be regarded as psychologically mediated and a psychodynamic folklore developed about it.

As there have been no controlled studies of psychiatric management of severe NVP such interventions are at this stage merely speculative. However, supportive psychotherapy would seem to be the bare minimum that should be offered to expectant mothers with NVP severe enough to cause personal distress or socio-occupational disruption. Here, the well-defined treatment goal aimed at present circumstances suits the self-limiting nature of the condition.

Tearfulness, irritability, lowered mood and sleep disturbances are common accompaniments to severe NVP. Such symptoms are probably secondary to the NVP but could be illustrative of an underlying affective disorder making antidepressants an attractive option. However both tricyclics and serotonin reuptake inhibitors are relatively contraindicated in the first trimester.

Symptoms of anxiety are invariably present in patients with severe NVP and anxiolytics may have a role. Again it is likely that severe NVP is anxiety provoking, but the possibility that anxiety is manifesting as nausea and vomiting must be considered. There is some incedental evidence that lorazepam can produce "immediate and marked improvement" (Trachttenberg 1991) in severe NVP. However benzodiazepines are not favoured in the first two trimesters because of a small but definite risk of teratogenic effects such as cleft palate.

There have been no controlled trials of any alternative approaches to severe NVP but acupuncture has been advocated.

Role of termination

With regard to the impact of severe NVP on the pregnancy, termination is a last resort when life threatening dehydration or ketosis supervenes or there is features of renal-liver-brain involvement. There are anecdotal accounts however of sever NVP leading to elective termination of pregnancy in the absence of such complication (Tylden 1968)

Conclusion :

In conclusion, while mild and moderate NVP can be viewed as physiologically and epidemiologically normal, both severe NVP and the total absence of NVP are probably abnormal, the former representing a greater challenge on account of its association with pregnancy loss and intrauterine growth retardation. While mental processes are sometimes postulated to underlay severe NVP, there is in all likelihood a complex interaction between physiological and emotional causative factors and the bodily and mental responses of the expectant mother to the disorder. Treatment should therefore espouse both medical and psychiatric components, the later comprising psychotherapy as the first line.

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MANAGED CARE?

The Ancients Sensed Science alone was not
Sufficient.
Yet clothed in myth, they worked their miracles free from
modern irks:
Quality Assessment,
Managed care (to name two most recent).
Nowadays, one can't Just be ``good'',
One must also be efficient.
One can't deny the part we played. We shirked
the dreary task, unaware that danger Lurked
in dollars and cents, `` Let's leave that
to the accountants '',We said.
We live in paradoxical age
We fertilize, We terminate;
Some we keep alive others not resuscitate.
The time has come for us to engage
Three questions plaguing these troubled day:
Who survives, who decides, and who pays?

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WE ARE HAPPY TO ANNOUNCE THE LUCKY WINNERS OF MEDIQUIZ - 3. OUR CONGRATULATIONS GOES TO THE WINNERS AND THANKS TO THE PARTICIPANTS.

THE WINNERS OF THE MEDIQUIZ - 3 ARE:

1. **DR. SHEIK MOHAMMAD NOOR-E-ALAM**
   408, NEW INTERNEE HOSTEL,
   SIR SALIMULLAH MEDICAL COLLEGE HOSPITAL.

2. **DR.DEVENDRA NATH SARKAR**
   CONSULTANT OF MEDICINE
   KURIGRAM SADAR HOSPITAL, KURIGRAM.

3. **DR. ATIQ**
   EMERGENCY MEDICAL OFFICER,
   BANGLADESH MEDICAL COLLEGE HOSPITAL.
   DHANMONDI, DHAKA.

4. **DR. KHAN GOLAM MOSTAFA**
   ASSISTANT REGISTRAR, WARD-11, UNIT-2,
   DHAKA MEDICAL COLLEGE HOSPITAL.

5. **DR.S.M. NURUL ABSAR**
   ASSISTANT REGISTRAR, WARD-11, UNIT-2,
   DHAKA MEDICAL COLLEGE HOSPITAL.

6. **DR. QUAZI RAKIBUS SULTAN**
   "MEDICARE CLINIC"
   JOARSHAHARA, DHAKA CANTONMENT, DHAKA.

7. **DR. A. K. M. MOSTAQUE AHMED**
   1, NOOR BOX LANE
   ARMANITOLA, DHAKA.

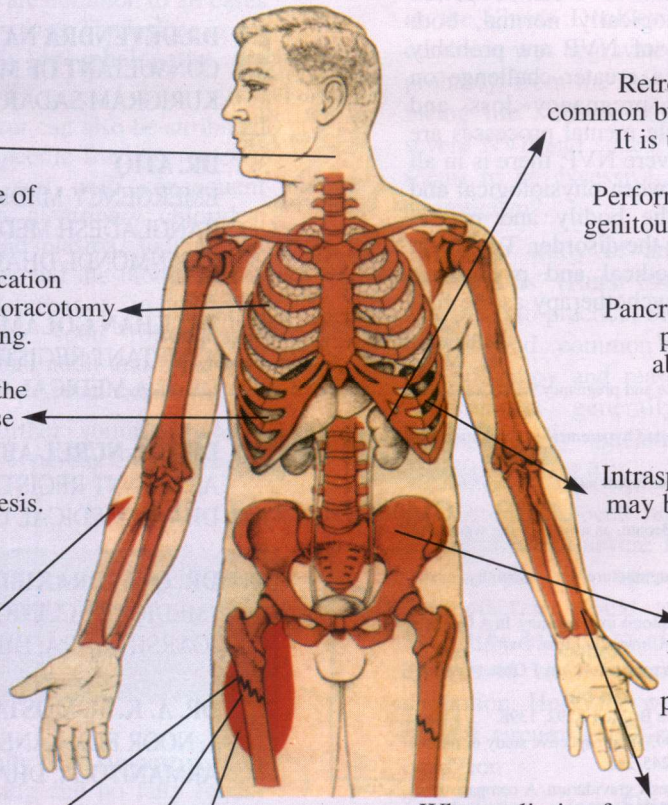
8. **DR. NAZNIN AKTER RUBY**
   207, MEDICAL COLLEGE LADIS HOSTEL
   KHULNA MEDICAL COLLEGE HOSPITAL, KHULNA.

9. **DR.M.M.A. SALAHUDDIN QUSAR (BIPLOB)**
   UDAYAN POLY CLINIC,
   280, NEW ESKATON ROAD, MOGHBAZAR, DHAKA.

10. **DR. MD. ABDUR RAZZAK**
    407/F, BANGABANDHU SHEIK MUJIB MEDICAL
    UNIVERSITY, DHAKA.

Clinical Highlights

CONTROL OF BLEEDING AND CORRECTION OF SHOCK IMPORTANT CONSIDERATIONS



Bleeding from cervical wounds is best controlled by direct digital pressure.

Hemothorax is a potential source of massive hidden blood loss (3000 cc. in each hemithorax). Complete post-traumatic opacification is an indication for immediate thoracotomy and surgery for control of bleeding.

Intra- abdominal bleeding from the liver or spleen is a common cause of post- traumatic blood loss. If hemoperitoneum is suspected, perform a fourquadrant paracentesis. If this is negative, follow with peritoneal lavage.

External bleeding from most sites is controlled by external pressure dressings or blood pressure cuff proximal to limb wound and inflated above systolic pressure.

The most frequent source of severe blood loss in multiple blunt injury cases is fracture.

Immediate splinting of fractures diminishes blood loss and prevents injury to local soft tissue, nerves, and blood vessels.

Retroperitoneal hemorrhage is less common but potentially more hazardous. It is usually caused by renal injury.

Perform emergency evaluation of the genitourinary tract in trauma patients with hematuria.

Pancreatic injury is suspected in the presence of persistent subacute abdominal discomfort after 6 to 12 hours in association with rising serum amylase.

Intrasplenic or intrahepatic bleeding may be responsible for unexplained blood loss and negative peritoneal lavage.

The most common cause of major retroperitoneal bleeding is fractured pelvis. Most patients respond to appropriate blood replacement and do not require operative intervention.

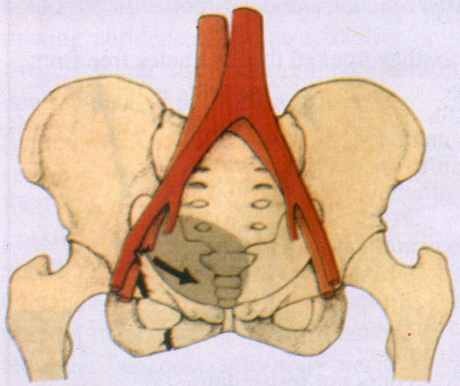
When splinting fractures, check peripheral pulses to ascertain presence of possible intrinsic vascular injury and need for prompt evaluation and repair.

Blood loss from fractures is 80 percent``complete" by six hours.

Enough blood and fluid should be replaced to prevent "sudden hypotension" four to six hours after injury.

Estimated blood loss from fractures

Pelvis	1500 to 2000 ml.
Femur	800 to 1200 ml.
Tibia	350 to 650 ml.
Humerus	200 to 500 ml.
Ribs	100 to 150 ml.



When retorperitoneal bleeding associated with pelvic fracture requires more than ten transfusions, retrograde aortography by means of the brachial artery will help identify any major arterial source of blood loss (likely to be a branch of the hypogastric artery deep in the pelvis). If lesser attempts at management fail to stop the bleeding, direct operative approach is indicated.

Self Assessment

A rash imposition from a lifestyle omission

A 31-year-old man with a history of alcohol abuse and psychiatric disease was admitted to the hospital because of a 3-week history of malaise and an asymptomatic rash on his legs. The patient, an unreliable historian, reported no medication use, fever, anorexia, weight loss, joint pain or swelling, cough, poor wound healing, bleeding, or unusual dietary habits.

The patient was slender but did not appear acutely ill. Vital signs were normal except for a regular heart rate of 96 beats per minute. Examination of neck, heart, lungs, and abdomen was unremarkable. Extremities examination showed bilateral confluent ecchymotic lesions, predominantly on the back of the thighs, with scattered bilateral circumferential perifollicular erythematous papules.

Complete blood cell count showed the following: haemoglobin 6.9 g/dL with normal red cell in dices,

reticulocyte count 4.4%, and serum folate 2.2 ng/mL (normal, > 3 ng/mL). White blood cell count and differential, platelet count, prothrombin time, partial thromboplastin time, bleeding time, and serum vitamin B_{12} level were normal. Results of a multichannel chemistry profile, thyroid function tests, and urinalysis also were normal. An HIV antibody test was negative. Additional laboratory testing and a skin biopsy were ordered.

WHAT IS YOUR DIAGNOSIS?

TURN THE PAGE FOR THE ANSWER

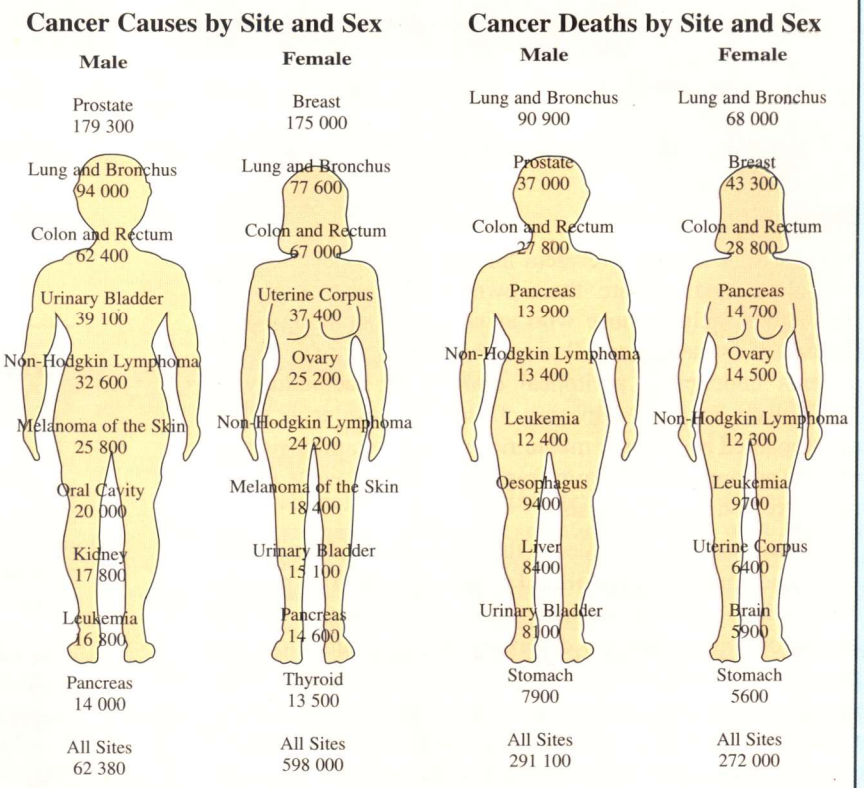
Leading Sites of New Cancer Cases and Deaths - 1999 Estimates*

The American Cancer Society (ACS) has issued its annual estimates of the expected numbers of new cases of cancer and numbers of deaths from the disease. The data are contained in two publications, *Cancer Facts & Figures* 1999 (from which the figure to the right is adapted) and *Cancer Risk Report,* and are available on the ACS Web site at www.cancer.org.

Lung cancer, which is expected to claim 158 900 victims this year, continues to be the leading cause of cancer death.

Estimating that 171 600 new cases will be diagnosed in 1999, the ACS is concerned that the decline in tobacco use by adults appears to have slowed and tobacco use by young people is actually increasing. About 87% of deaths from lung cancer and about 30% of all deaths from cancer can be attributed to smoking, says the ACS.

*Excluding basal and squamous cell skin cancer and carcinomas in situ except urinary bladder.



JAMA, February-3, 199-Vol. 281, No. 5

Self Assessment, Continued

The Diagnosis: Vitamin C deficiency

The additional laboratory testing detected a serum vitamin C level of 0.2 mg/dL (normal, 0.3 to 2 mg/dL). Skin biopsy of the right thigh revealed nonspecific pervascular inflammation and extravasation of red blood cells into the papillary dermis. Although the patient was young and able to conduct activities of daily living, vitamin C deficiency was suspected on the basis of his history of alcoholism and psychiatric disorder and, as he later disclosed, a diet severely deficient in fresh fruits and vegetables for an extended period. Treatment consisted of oral ascorbic acid, 400 mg/day up to a total of 4 g, then 100 mg/day. Significant improvement was noted after 10 days.

At diagonosis. On day 10 of treatment.

Discussion

Adult scurvy is most prevalent among elderly persons who live alone and prepare their own food. Other high-risk individuals include those who avoid acid-containing foods because of dyspepsia or reflux esophagitis, food faddists, and patients undergoing peritoneal dialysis or haemodialysis. Alcoholism is a predisposing factor because it is often accompanied by chronic malnutrition. Hypovitaminosis C—related purpura results from fragility of vessel walls due to defective collagen synthesis.

The most evident early clues to the diagnosis are found in the skin and include perifollicular hyper-keratotic papules surrounded by a hemorrhagic halo, abnormalities of hair formation with corkscrew deformity and fragmentation, and purpura typically on the posterior aspects of the lower extremities, which coalesces to form ecchymosis. These classic findings usually become apparent only after at least 3 months of severe or total vitamin C deficiency.

Other manifestations include gingival and ocular haemorrhage, sicca syndrome, femoral neuropathy due to haemorrhage in the femoral sheath, depression, and arthritis. Haemorrhage may occur in the muscles of the arms, legs, and joints. In 75% of patients, anaemia develops as a result of blood loss into tissue, coexisting dietary deficiency, altered absorption and metabolism of iron and folate, gastro-intestinal blood loss, and intravascular haemolysis. Cardiac complications range from reversible ST-segment and T-wave changes on electrocardiography to sudden death.

The clinical manifestations of vitamin C deficiency can easily mimic a cutaneous leukocytoclastic (hypersensitivity or small-vessel) vasculitis, deep vein thrombosis, or systemic bleeding disorders, often leading to a delay in diagnosis. Because some complications of scurvy can cause sudden death, prompt diagnosis and treatment are essential.

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Wren and the warm sack saga

Sir Christopher Wren, the great 17th century English architect, is best remembered as the designer of St Paul's Cathedral in London. He also played a role in the rebuilding of London after the great fire of 1666 and was a professor of astronomy at Oxford University and an enthusiastic scientist. In fact, Wren is credited with administering the first successful intravenous anaesthetic in 1659.

To satisfy his curiosity about both opium and alcohol, Wren injected a dog with opium in warm sack (sherry). The dog reportedly was stupefied. While this venture was considered an interesting oddity at the time, it was not recognized as an important contribution to the science of anaesthesiology until the 19th century.

Resident Round

Pulmonary Hydatid cyst as a cause of recurrent haemoptysis and responding To Treatment with albendazole

Introduction

Pulmonary hydatid cysts infrequently present as multiple and bilateral diseases. They are usually asymptomatic but when a cyst ruptures, a massive leak of hydatid fluid could result in anaphylactic shock and a minor leak can communicate with a bronchus and lead to superinfection and abscess formation. Haemoptysis is rare in hydatid disease. The treatment of pulmonary hydatid is careful surgical removal of the cyst. Surgery however can be technically difficult in patients with multiple and bilateral disease and between 10 to 30% of patients will anyway have recurrence of the cyst within 5 years of surgery. Furthermore, the perioperative mortality increases from 1% to 20% in successive surgeries. Since mid 1980s, chemotherapy using the benzimidazole compounds, notably albendazole have proved to be either totally or partially effective in the treatment of some of these cases. We report here a case of pulmonary hydatid cysts with uncommon clinical presentation and who responded to treatment with albendazole.

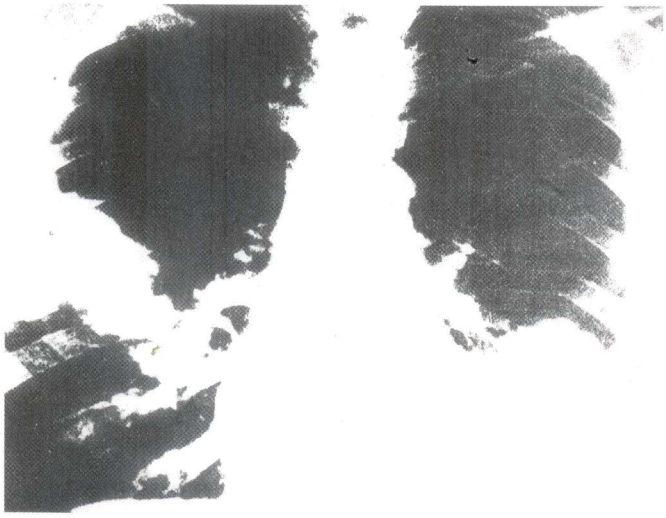

Figure 1. A postero-anterior and lateral films of bilateral pulmonary hydatid cysts.

Case Report

T.M, a 26 year old male when first came to hospital 2 years ago with complaints of cough and intermittent haemoptysis- he was empirically started on anti-TB medication which he took for one and half years but showed no improvement. Instead, his symptoms got progressively worse with frequent and frank haemoptysis, low grade fever, left sided chest pain and weight loss. He was brought and admitted to hospital where he had a chest x-ray taken for the first time. The chest x-ray showed bilateral, well circumscribed oval and circular lesions and obliteration of the left costophrenic angle (Figure 1). Sputum smear examination for acid fast bacilli (AFB) was repeatedly negative and sputum culture grew aspergillus species. A diagnosis of multiple fungus balls (aspergillomas) was entertained and subsequently referred to the Chest Unit for further evaluation and management.

Investigations revealed, Hgb = 13.9gm%, WBC = 7000mm^3, ESR 12mm in the 1st hr. Urine analysis, liver and renal function tests were all normal. Sputum smear examination was negative for AFB. Bronchoscopic aspirate grew aspergillus species. The cytological examination was negative for malignant cells.

Ultrasound of the pulmonary masses were reported as cystic in consistency but there were no daughter cysts or hydatid sand observed. With a diagnostic impression of multiple pulmonary hydatid cysts with superinfection, patient was started on antibiotics (ampicillin, gentamycin) and albendazole 400 mg PO twice a day. Ten days after initiation of treatment, the patient started to show signs of improvement and by the end of one month he was completely free of symptoms. He was given another course of albendazole for 4 weeks as an outpatient and his chest x-rays after 2 months of treatment showed complete resolution of the cyst fluid (Figure 2).

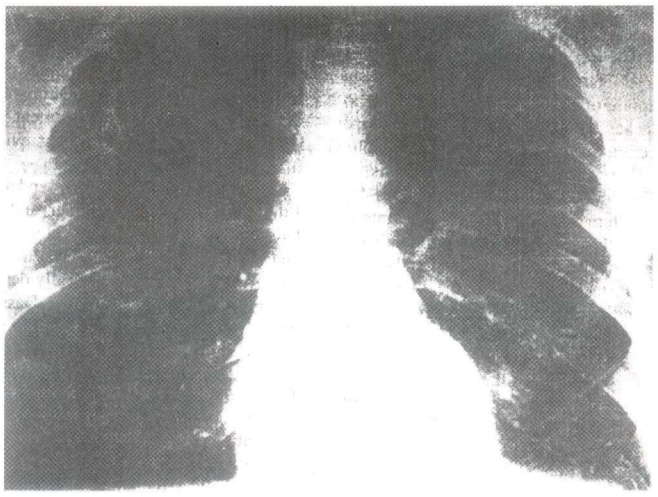

Figure 2. Complete resolution of cyst fluid with a residual surrounding halo, 2 months after treatment with albendazole.

Discussion

The patient remained a diagnostic problem for 2 years due to the uncommon clinical presentation and lack of diagnostic facilities. The definitive diagnosis of pulmonary hydatid cyst requires an ELISA test which is the most sensitive and specific serologic test. Indirect Hemagglutination Test (IHA) is positive in about 60% of cases. Unfortunately these tests are usually kept in reference laboratories and are not easily available for routine use. Most patients with cystic hydatid disease are asymptomatic until such-time the cyst ruptures spontaneously or as a result of infection and the patient develops cough productive of purulent sputum that contains fragments of hydatid membrane. This patient most likely had a rupture of a cyst with communication to a bronchus leading

to a continuous superinfection and erosion of surrounding blood vessels resulting in gross haemoptysis.

The finding of aspergillus species from the sputum and bronchoscopic aspirate and the fact that pulmonary aspergilloma tend to occur in a preformed cavity and also infect a preformed cyst makes the diagnosis of aspergilloma tempting. However, aspergillomas commonly present as a solitary mass with typical air crescent sign within the cavity. Besides, ultrasound examination revealed multiple cystic lesions rather than solid mass lesions. These findings therefore supported a diagnosis of hydatid cyst rather than aspergilloma. The finding of aspergillus species in this patient could have been due to endobronchial colonization rather than infection by the fungus.

The treatment of cystic hydatid disease is principally surgical. Surgery however is associated with significant perioperative mortality and recurrence. Besides, multiple bilateral cysts and disseminated hydatid disease are technically difficult to operate. The benzimidazole compounds, initially flubendazole and mebendazole, had been tried for the treatment of cystic hydatid disease but the results were discouraging owing to the poor concentration of the drugs both in serum and the cysts . Later on however, encouraging results were obtained using albendazole and this was accounted by the presence of high concentration of the active metabolite, albendazole sulphoxide both in the serum and the cysts. Analysis of pooled data of all drug trial using albendazole between 1983 and 1989 on 500 patients demonstrated an overall success rate of 80% (30% cure and 50% reduction in size). The drug safety profile included transient hepatotoxicity which rarely required discontinuation of the medication. This patient did extremely well with the treatment.

Getachew Aderaye, 1998, Ethiop Med J, 36

Medi Tips

Tricks for zeroing in on abdominal pain

Acute abdominal pain is a common problem. Despite the increasing use of imaging procedures, the hallmark of correct diagnosis continues to be a detailed history and thorough physical examination.

Careful observation of the patient and gentle percussion and palpation of the abdomen looking for tenderness, guarding, and rigidity are well-known techniques. The psoas and obturator signs may also be useful. Searching for rebound tenderness is not needed and may be unnecessarily painful for the already ill patient.[1,2]

We would like to describe five additional diagnostic maneuvers that may be helpful. As an aside, their use also increases the intellectual enjoyment of physical diagnosis.

- **Heel-drop jarring test**[3]**:** The patient stands, then goes up on his or her toes for 15 seconds, and then comes down with full weight on his or her heels. The patient is then asked if this maneuver causes abdominal pain and, if so, where. The location of the pain indicates underlying infection or inflammation in that part of the abdomen.
- **Abdominal wall tenderness test**[4] **:** While the patient is supine with abdominal muscles relaxed, the examiner palpates the tender spot. The patient is then asked to tense the abdominal muscles, and the tender spot is palpated once again. If the tenderness is worse, the abdominal wall muscles are most likely the source of the pain, rather than the underlying abdominal cavity.
- **Hover sign**[5] **:** The examiner places his or her hand just above the area of abdominal pain or touches this area with the fingertips. If the patient grabs the hand, grimaces in anticipation of more pain, or guards the tender area with his or her hand, the abdominal wall is the site of pain.
- **Cough sign** [6]**:** The patient is asked to cough and then questioned as to whether this causes abdominal pain and, if so, where. If pain is reproduced in a specific location, this is a sign of underlying peritoneal irritation.
- **Closed eyes sign** [7] **:** The examiner observes the patient's eyes before and during the abdominal examination. Those with specific intra-abdominal disease keep their eyes open, fearful that the examining hand will cause even more pain. Those with less serious, nonspecific abdominal pain problems tend to keep their eyes closed.

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2. **Moustafa MH, Newton E**. Does this patient have appendicitis: (Letter) JAMA 1997;277(8):625; discussion 626-7
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4. **Thomson H, Francis DM**. Abdominal wall tenderness; a useful sign in the acute abdomen. Lancet 1977;2(8047):1053-4
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6. **Bennett DH, Tambeur LJ, Campbell WB**. Use of coughing test to diagnose peritonitis, BM 1994;308(6940):1336
7. **Gray DW, Dixon JM. Collin J**. The closed eyes sign: an aid to diagnosing nonspecific abdominal pain. BMJ 1988; 297(6652):837

Drug induced Side-Effects

Cardiovascular System

1) Acute Chest Pain (non-ischaemic)

Bleomycin

2) Exacerbation of Angina

α-blockers
Ergotamine
Hydralazine
Minoxidil
Oxytocin
β-blocker withdrawal
Excessive thyroxine
Methdysergide
Nifedipine
Sumpatriptan, Vasopressin

3) Arrhyhmia

Adriamycin
Astimazole
Anticholinesterase
Cisapride
Emetine
Guanethidine
Lithium
Pentamidine
Thioridazine
Sympathomimetics
Theophylline
Verapamil
Anti-arrhythmic drugs
Atropine
β-blockers
Daunorubicin Digitalis
Erythromycin
Ketaserin
Papaverine
Phenothiazines
Probucol;
Terfenadine
Thyroid hormone

4) AV Block

Clonidine
Verapamil
Methyldopa

5) Cardiomyopathy

Adriamycin
Daunorubicin
Lithium
Sulphonamide
Alcohol
Emetine
Phenothiazines
Sympathomimetics

6) Oedema / Conngestive Cardiac Failure

β-blocker
Carbenoxolone
Oestrogen
Mannitol
Phenylbuyazone
Verapamil
Calcium channel blocker
Diazoxide
Indomethacin
Minoxidil
Steroids

7) Hypertension

Clonidine withdrawal
Cyclosporine
NSAIDs (some)
Sympathommimetics
Corticotrophin
Glucocorticocoid
Oral contraceptives
Monnoamine oxidase inhibitors with sympathomimetics
Tricyclic antidepressants with sympathomimeetics

8) Pericardial effusion

Minoxidil

9) Thromboembolism

Oral contraceptives

Respiratory System

1) Airway obstruction (bronchospasm; asthma)

Adenosine,
β-blocker Cholinergic drugs
Penicillin
Streptomycin
Cephalosporin
NSAIDs
Pentazocine
Tartrazine (drugs with yellow dye)

2) Cough

ACE inhibitors

3) Nasal congestion

Decongestant abuse
Isoprotenolol
Reserpine
Guanethidine
Oral contraceptives

4) Pulmonary oedema

Contrast media
Hydrochlorthiazide
Interleukin 2
Heroin
Methadone
Propoxyphene

5) Pulmonary hypertension

Fenfluramine

6) Pulmonary infiltrates

Acyclovir
Azothioprine
Busulphan
Cholorambucil
Gold
Methotrexate
Mitomycin C
Procarbazine
Amiodarone
Bleomycin
Carmustine (BCNU)
Cyclophosphmide
Melphalan
Methysergide
Nitrofurantoin
Sulphonamide

7) Respiratory depression

Aminoglycosides
Opiates
Sedatives
Hypnotics
Polymyxins
Trimethaphan

The LEARN model for improving cultural and socio-economic provision of healthcare

L Listen to your patient from his or her cultural and socio-economic perspective

E Explain your reasons for asking for personal information (eg, lifestyle issues, family issues)

A Acknowledge your patient's concerns

R Recommend a course of action

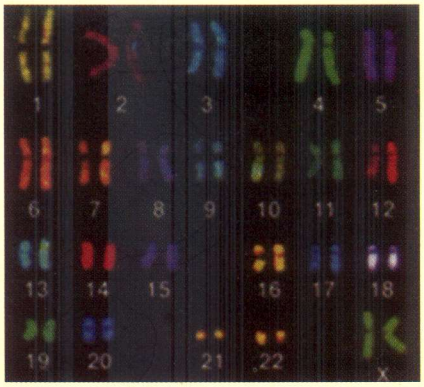
N Negotiate a plan that takes into consideration your patient's cultural and socio-economic norms and personal lifestyle

MediNews

From Internet /Journals

"TALKING" GENETICS GLOSSARY

As the Human Genome Project hurtles toward its goal to obtain a blueprint for all human genes within the next few years, health care professionals and the public alike will be wrestling with the genetic terms and concepts needed to understand recent advances in human genetics.



The "Talking" genetics glossary offers text, audio clips, and illustrations to explain such terms as spectral karyotype (SKY), a technique that labels each chromosome with a different colour to better identify chromosome abnormalities.

To help those seeking such information, the National Human Genome Research Institute has launched an online "talking glossary of genetics," available on the Internet at http://www.nhgri.nih.gov/DIR/VIP/Glossary/. The project combines text, audio, and illustrations of selected terms to help explain nearly 200 essential genetics terms.

One unique feature of the glossary is the use of in-depth audio clips of prominent experts in genetics, molecular biology, and medicine explaining such terms as *gene therapy* and *positional cloning* in straightforward, nontechnical language.

JAMA, FEBRUARY 17, 1999 - VOL 281, NO. 7

PLANT BASED VCCINES MOVE A STEP CLOSER

In the future eating a potato or banana will not just provide nutrients but may also provide protection against infectious diseases. The first clinical trials of plant based immunotherapies show that this technology is very close to application.

In one study Julian Ma and colleagues from Guy's Hospital, London, engineered a tobacco plant to produce antibodies against *Streptococcus mutans*-an oral bacterial infection that contributes to dental caries *(Nature Medicine 1998;4:601-6).* When they applied a solution of the antibody to subjects' teeth—which had previously been sterilised-they found bacteria were not able to recolonise the mouth up to four months later because of the presence of the antibody. This effect is known as passive immunization.

A second study, by Carol Tacket and colleagues at the Center for Vaccine Development, Baltimore, reports the results of a trial of a potato based vaccine intended to prevent infection by *E. coli (Nature Medicine 1998;4:607-9).* Even healthy volunteers ate raw potato that had been genetically engineered to produce a part of the toxin released by *E. coli.* Antibody secreting cells derived from gut associated lymphoid tissues appeared in the blood circulation of the volunteers a week after the oral vaccination.

Dr. Tacket and colleagues write: "Compared with vaccine delivery by injection, oral vaccines offer the hope of more convenient immunisation strategies and a more practical means of implementing universal vaccination programmes throughout the world.

In the same issue of *Nature Medicine,* Takeshi Arakawa and William Langridge from the Center for Molecular Biology and Gene Therapy in Loma Linda, California, write: "These findings move plant based vaccines a step closer to practical application for prevention of infectious diseases in humans." They add: "Plant based production of immunotherapeutic proteins may soon become economically competitive enough to supplement or even replace more conventional vaccine production systems."

Two of the volunteers who ate raw potato in the second study complained of nausea. Recent research has shown that transgenic potato tissues cooked until soft retain about 50% of the antigen. This suggests that if the recombinant protein production levels in the plant tissue are high and overcooking of the tuber is avoided, the viability of mucosal vaccines can to some extent be protected. However, the immunogenicity of the vaccine potato when cooked has still to be evaluated.

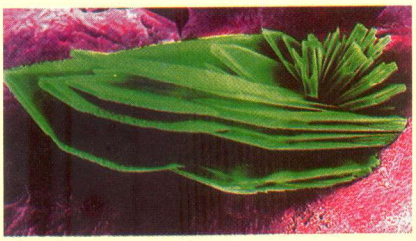
Researchers are now investigating banana as an alternative to potato for vaccine production. Banana is the world's fourth largest crop, and as they can be eaten without cooking they would be an ideal plant species for vaccine production. Another advantage is that even infants can eat raw banana.

www.bmj.com

DOCTORS ADVISED TO TAKE SPECIAL CARE WITH HUMAWN ALBUMIN

The Committee on Safety of Medicines has advised doctors to restrict the use of, and take special care when using. human albumin after concerns that far from saving life the preparation may actually increase mortality.

A systematic review by the Cochrance Group published last year (BMJ 1998,317:253-40) of 23 randomised controlled trials, including 1419 critically ill patients with hypovolaemia, burns, and hypoalbuminaemia, found that the risk of death in the group treated with albumin was significantly higher than in patients who received either crystalloids or no treatment. The pooled difference in the risk of death with albumin was 6% (3% to 9%). An expert working group set up by the Committee on Safety of Medicines to examine the findings has now concluded, however, that there is "insufficient evidence of harm to warrant withdrawal of albumin products from the market" and that the effect of albumin on mortality can "only be answered by conducting large, purpose designed, randomised, controlled clinical trials."



Albumin: possible association with increased mortality

Nevertheless, it has recommended that the indication for human albumin solutions should focus on the use of albumin to replace lost fluids rather than the underlying illness resulting in hypovolaemia and that hypoalbuminaemia in itself is not an appropriate indication.

It also recommended that product infromation should contain warnings about the risks of hypervolaemia and cardiovascular overload and emphasise that monitoring in patients receiving albumin shuld be undertaken. BMJ VOL. 318 19 JUNE 1999

HEAT AND HEART ATTACK

Researchers at the University of Athens, Greece, report that they have, for the first time, measured temperatures inside patients' coronary arteries and linked elevated temperatures with a risk of myocardial infarction (MI).

The study included 90 patients whose coronary arteries were examined with a tiny thermometer attached to the tip of a catheter. Half were atherosclerosis-free and served as controls. Of the remaining half, 15 had stable angina, 15 had unstable angina, and 15 had suffered an MI within hours of the examination.

In disease-free patients, five temperature readings taken at sites on a healthy artery wall showed an average temperature 0.65°F higher than the oral temperature. For those with heart disease, temperatures at plaque sites on arteries were higher than at healthy sections of artery. Plaque temperatures were 0.19°F higher than at healthy artery sites in patients with stable angina, 1.23°F higher in those with unstable angina, and 2.65°F higher in patients who had just had an MI.

Researchers theorize that the use of thermography to record plaque temperatures could help physicians identify patients at highest of risk of MI.

JAMA, MAY 12, 1999 - VOL 281, NO. 18

AN EGG A DAY IS NOT HARMFUL

Two prospective studies covering almost a decade have shown that healthy people did not increase their risk of heart disease or stroke by eating one egg a day (*JAMA* 1999,281:1387-94).

It's OK to go to work on an egg

Its not eggs but other dietary and lifestyle choices that are the problem. "Egg consumption was positively associated with smoking, lower physical activity, and a generally unhealthy eating pattern," the researchers report.

Men and women who ate eggs were more likely to eat bacon, and men were more likely also to consume whole milk, red meat, and bread, and less likely to consume skimmed milk, chicken, vegetables, and fruit. Findings were less clear in women. Study coauthor Dr Frank B Hu, a nutritional epidemiologist at the Harvared School of Public Health, said : "Eggs are a controversial food in the nutrition community. They are high in cholesterol. One egg contains about 210 mg of cholesterol. Because of that, it was believed that egg consumption caused heart disease, although there are no direct scientific data."

Many studies have looked at the effect of egg consumption on serum cholesterol, but few if any have looked at the link between egg consumption and heart disease.

The study, part of two ongoing studies at Harvard, included 80000 women in the nurses' health study and 40 000 men in the health professionals' follow up study. Participants answered lengthy questionnaires about helath status and dietary habits.

People were included in the egg study if at outset they did not have cardiovascular disease, diabetes, hypercholesterolaemia, or cancer. Outcome measures of non-fatal myocardial infarction, fatal coronary heart disease, and stroke were related to participants' reported egg consumption, which ranged from almost none to two or more per day.

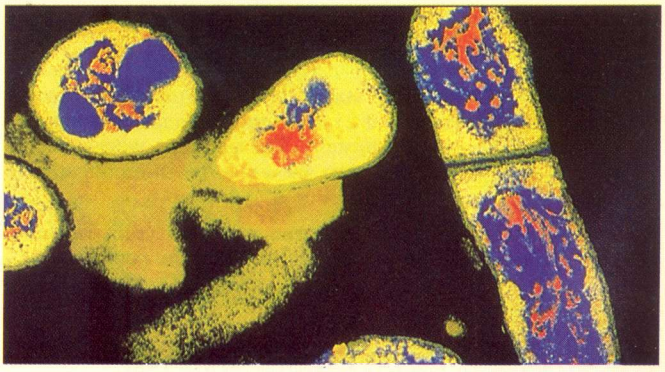
One egg a day did not have an impact on heart disease or stroke in healthy men and women. Either the effect of dietary cholesterol from eggs is not as great as was thought, or it is counterbalanced by beneficial nutrients in eggs or dietary cholesterol is so high in the usual Western diet than an egg here or there doesn't matter.

Only in a subgroup of people with diabetes was there an increased risk of coronary heart disease.

BMJ VOL. 318 17 APRIL 1999

RESEARCHERS FIND GENETIC BASIS FOR SUSCEPTIBILITY TO MYCOBACTERIA

New research has suggested that there is a genetic reason why some people are more susceptible to infections with non-tuberculous mycobacteria.



A genetic defect underlies susceptibility to mycobacterial infection

Researchers at INSERM, in Paris, investigated disseminated non-tuberculous mycobacterial infection, in which otherwise healthy individuals develop overwhelming infections with mycobacteria that normally are not virulent (*Nature Genetics* 1999;21;370-8). *M. tuberculosis* and *M. leprae*- the organisms that cause tuberculosis and leprosy-are the most pathogenic mycobacteria, but most bacteria in the class are relatively harmless. Rare individuals develop disseminated infections with normally non-virulent non-tuberculous mycobacteria. Some develop fatal infections after vaccination with Bacille Calmette-Guérin (BCG).

The researchers studied 18 people from 12 unrelated families with idiopathic reactions to vaccination with BCG or disseminated non-tuberculous mycobacterial infection. Previous investigations had shown that the receptor for interferon gamma—a cytokine with a central role in combatting infections—was implicated. The Researchers found homozygous mutations in the DNA regions encoding for the interferon receptor.

BMJ VOL. 318 17 APRIL 1999

NEW MALARIA VACCINE SHOWS PROMISE

Malaria infects about 400 million people a year and kills 3 million annually. The development of an effective malaria vaccine has become an international health priority.

An experimental malaria vaccine designed to protect the host from each stage of the parasite's life cycle has shown promise in animal trials *(Proceedings of the National Academy of Sciences* 1999;96:1615-20).

Researchers from the US Cent Centers for Disease Control and Prevention in Atlanta, Geogria, have created a recombinant, multivalent vaccine against *Plusmodium falciparum*, the deadliest malaria parasite. This vaccine differs from previous vaccines because it contains multiple antigens and targets the parasite at several stages in its life cycle.

Construction of a successful vaccine has been hampered by the complexity of the parasite's life cycle. In addition to both the mosquito vector and vertebrate phases, the parasite undergoes multiple incarnations within its host. For instance, it has an asextual sporozoite phase in which it freely circulates within the bloodstream, a gametocytic phase within red blood cells, a schizont phase, and a merozoite phase within hepatocytes. The parastie's identity changes through each of these stages-including changes in surface antigens-and this presents a challenge to vaccine development.

Additionally, the parasite cloaks itself in different proteins during the erythrocytic and hepatocytic phase, and these membrane proteins also undergo phenotypic variation. Therefore a vaccine directed against a single epitope or which targets only one phase of the parasite's life cycle may not be sufficient to induce protective antibodies.

The centres' scientists, led by Altaf Lal, took advantage of the parasite's complicated life stages by constructing a vaccine which combined segments of 21 different *P faliciparum* peptides into a single recombinant protein. The peptides were selected because each of them had been shown to be immunogenic in previous vaccine trials.

Different parts of the host's immune system-B cells, helper T cells, and cytotoxic T cells-were activated by the peptides.

The scientists plan to test the vaccine on non-human primates before proceeding to human trials. www.sciencemag.org

WOMEN WITH HEART DISEASE CAUTIONED ABOUT HRT (HORMONE REPLACEMENT THERAPY)

Postmenopausal women with a history of coronary artery disease probably should not start taking hormone replacement therapy (HRT), according to a study present at the annual meeting of the American College of Cardiology (7-10 March, New Orleans, Louisiana). The report is the second released within a year to question the use of HRT in postmenopausal women with heart disease.

Duke University researchers led by Dr Karen Alexander, performed an observational analysis of 1875 postmenopausal women with coronary artery disease. The study results were culled from a previous investigation, the coumadin-aspirin reinfarction study. The Duke University researchers found that of 111 patients who started HRT after a myocardial infarction 33% were subsequently hospitalised for unstable angina within a year. No deaths were reported in this group however.

Women who were taking hormone replacement therapy before their first myocardial infarction and who continued it after a myocardial infarction also had a high rate of hospitalisation for unstable angina. A total of 413 patients fell into this category; 21% of them were admitted for unstable angina within the first year, and four (1%) of them died.

In contrast, of the 1333 women who were never on HRT, only 17% were hospitalised for unstable angina in the year after their heart attack, and 4% of them died. The death rates were not considered statistically significant across the groups. It is unclear why HRT would increase the risk of myocardial infarction but the thrombogenic properties of oestrogens are likely to play a part.

The Duke University study is the second to challenge the conventional medical wisdom which assumes that HRT is nearly always cardioprotective.

The Duke University results are similar to those found in an earlier study published in *JAMA* (1997;277:1281-6).

www.bmj.com.

AIDS NOW WORLD'S FOURTH BIGGEST KILLER

AIDS is now the fourth leading cause of death in the world, and the number one killer in Africa, according to figures released this month by the World Health Organization (WHO). The disease has moved up several notches from last year's ranking as seventh leading killer worldwide, according to WHO's latest World Health Report. Only ischemic heart disease, cerebrovascular disease, and acute lower respiratory infections outrank AIDS on the international death list. In Africa, AIDS caused an estimated 1,830,000 mortalities in 1998, twice as many as due to malaria, which is now relegated to the number two spot on the continent's roster of lethal diseases.

LEADING CAUSES OF DEATH WORLDWIDE IN 1998

(1997 rank in parentheses)

1. Ischemic heart disease (1)
2. Cerebrovascular disease (2)
3. Acute lower respiratory disease (3)
4. HIV/AIDS (7)
5. Chronic obstructive pulmonary disease (5)
6. Diarrhoeal diseases (6)
7. Perinatal conditions (new category)
8. Tuberculosis (4)

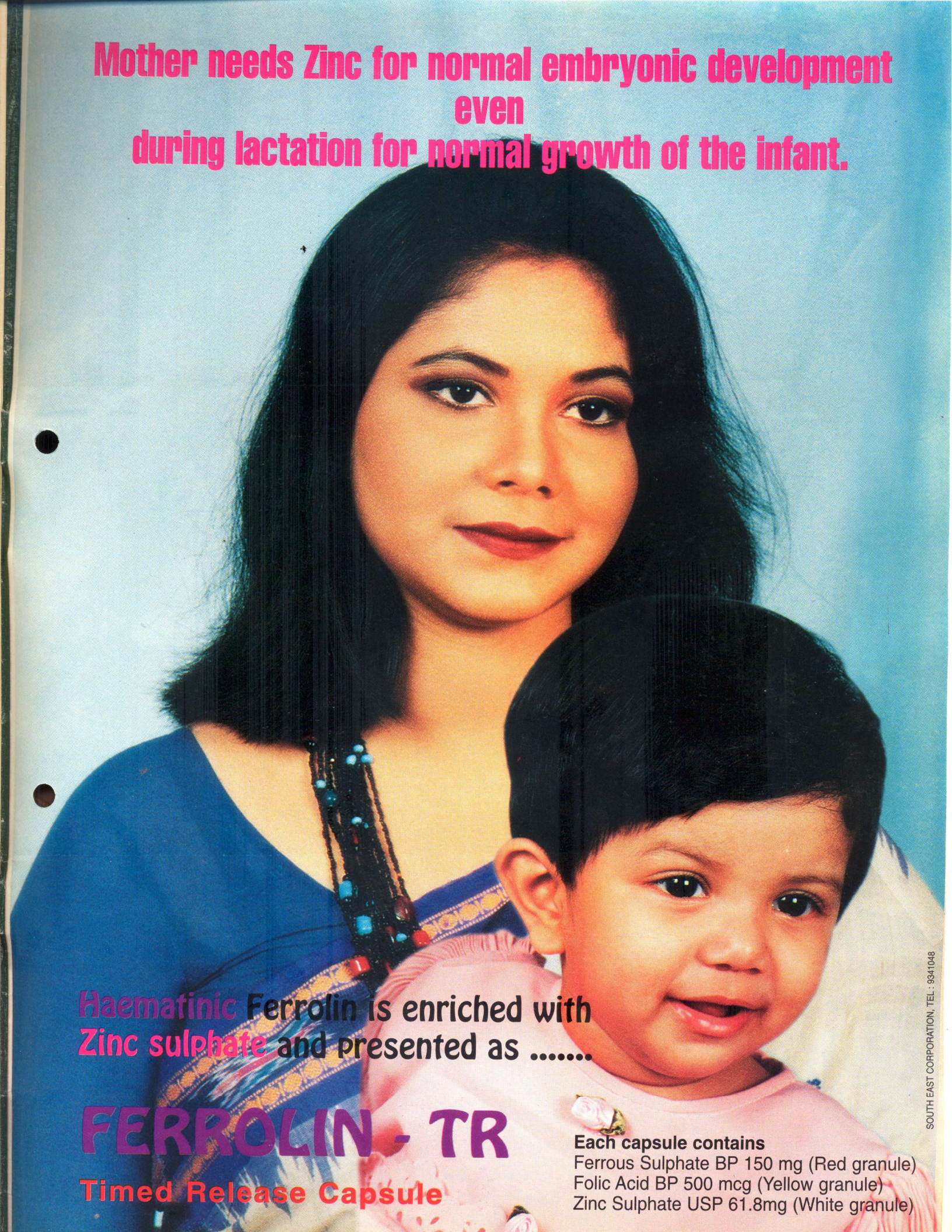
Bernhard Schwartlander, senior epidemiologist for UNAIDS, the United Nations AIDS program, says that some of the change in disease ranking is due to new and improved methodologies for estimating disease mortality, which have revised estimates of some disease downward while AIDS cases have been skyrocketing. Nevertheless, the new figures dramatically vindicate warnings late last year by UNAIDS that the epidemic is still raging out of control *(Science,* 4, December 1998, p. 1790). UNAIDS estimates that new infections by HIV, the virus that causes the disease, are increasing by at least 6 million each year.

SCIENCE VOL 284 14 MAY 1999

SOUTH EAST CORPORATION

Dolly, the first animal to be cloned from a single adult cell, shows off her first lamb, Bonnie, born at the Roslin Institute, Edinburgh. Dolly mated naturally with a Welsh mountain ram from the same Finn Dorset breed. Dolly was created in July 1996 from a cell taken from a 6 year old ewe. Harry Griffin, assistant director at Roslin, said that Dolly and Bonnie would live out a "celebrity lifestyle," being introduced to occasional scientific visitors. www.bmj.com.

Mother needs Zinc for normal embryonic development even during lactation for normal growth of the infant.



Haematinic Ferrolin is enriched with Zinc sulphate and presented as .....

FERROLIN - TR

Timed Release Capsule

Each capsule contains
Ferrous Sulphate BP 150 mg (Red granule)
Folic Acid BP 500 mcg (Yellow granule)
Zinc Sulphate USP 61.8mg (White granule)

SOUTH EAST CORPORATION, TEL : 9341048