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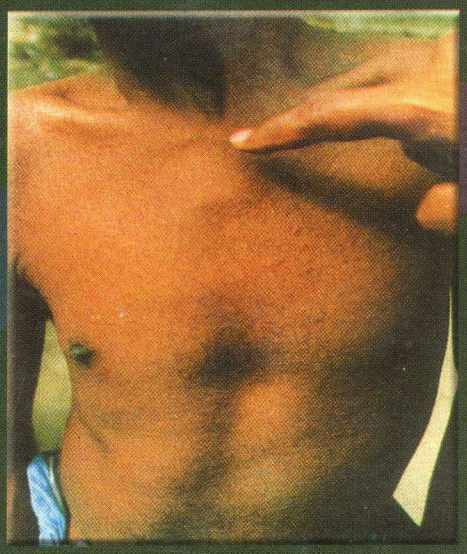
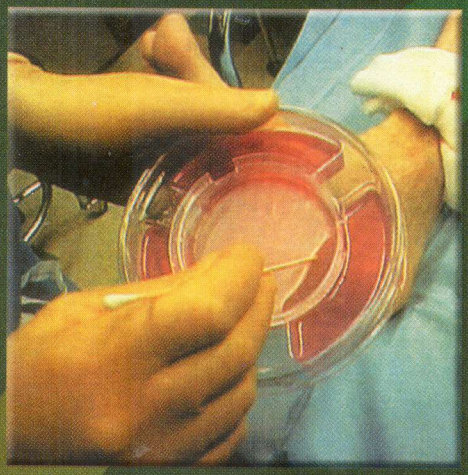
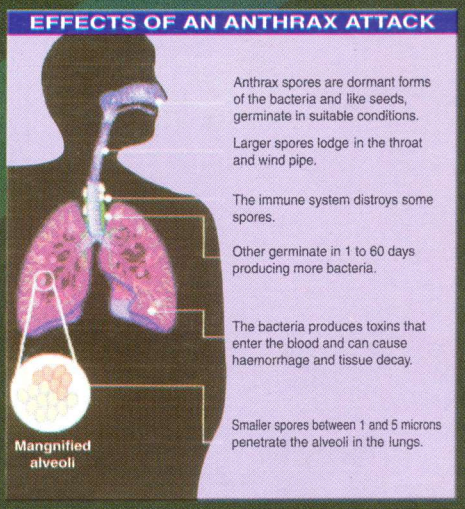
Chronic Arsenic Toxicity Through Contaminated Drinking Water in Bangladesh





Bioengineered Skin

Bacillus Anthrax--- Re-Emerging Issue



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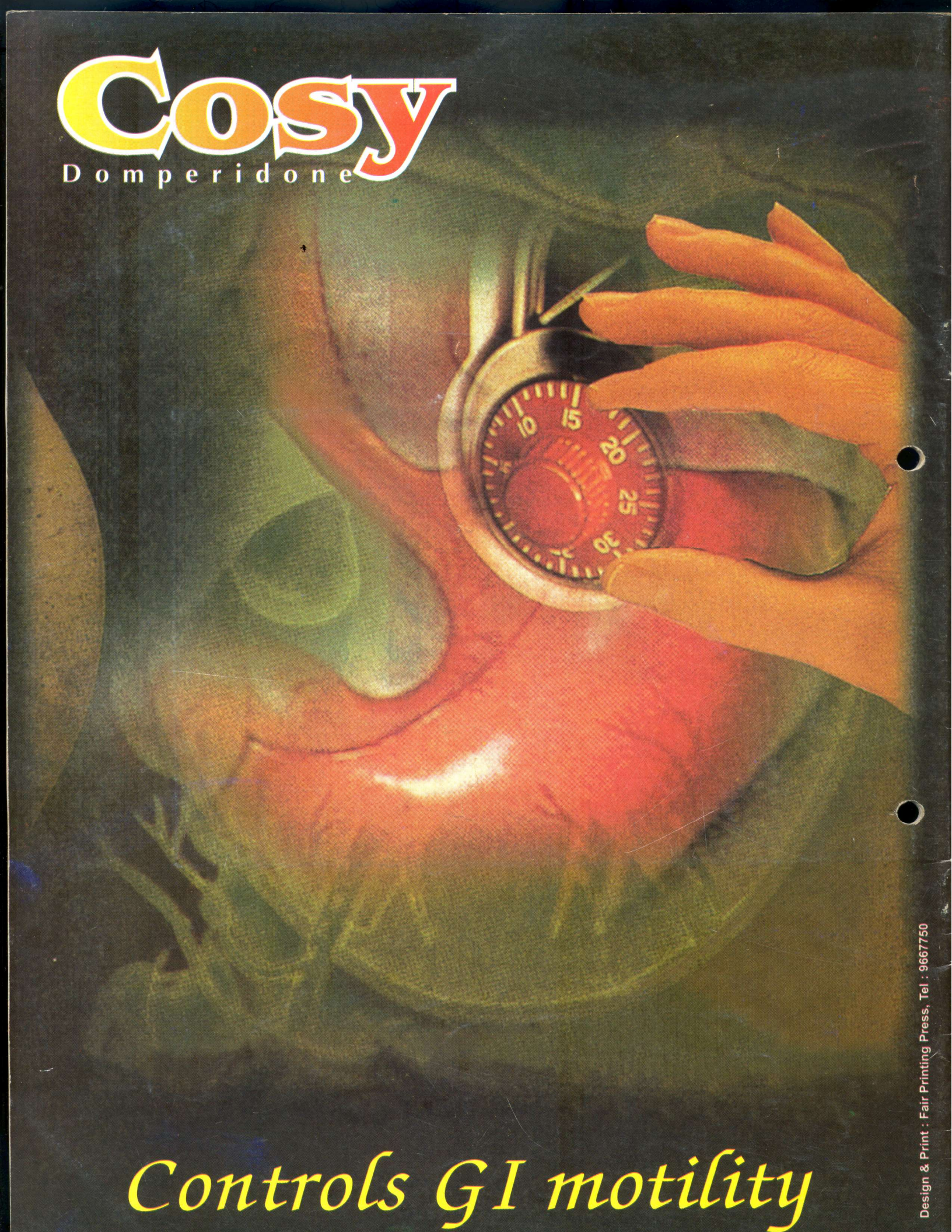

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Procap

Omeprazole

Proton Pump Inhibitor with Competence and Precision

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COVER ILLUSTRATION

Pictorial depiction of Arsenic Toxitity by a picture of a man with typical skin manifestation all over the body, Bioengineered skin by a picture of an engineered dermal component, Bacillus Anthrax–Re-Emerging Issue by a figure showing effects of attack of inhalation form of anthrax.

PUBLISHER'S NOTE

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Editorial

"Eid Mobarak" and *New Year's Greetings* to the esteemed readers of "The ORION". In line with our programs of Continued Medical Education we try to adopt innovative ways to serve the health care Professionals. Publication of "The ORION" reflects our concerted efforts to keep doctors community abreast of the recent medical developments, updated documents and information for better management of diseases and alleviation of sufferings.

It is our pleasure and privilege in having two dignified and well experienced professionals to be with us as the consultant editor and the guest editor which will enrich "The ORION" from this issue. We are also having one new member in the Advisory Board and another new member in the Review Board.

Considering the opinions of the valued readers we decided to focus in this issue, arsenic toxicity in Bangladesh by "Chronic Arsenic Toxicity through Contaminated Drinking Water in Bangladesh: Magnitude of the Problem, Health Effects and Detoxification," new dermatological development by "Bioengineered Skin," recent re-emerging infection by "Bacillus Anthrax–Re-Emerging Issue".

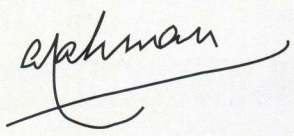
In Bangladesh the arsenic concentration in drinking water is very much higher than the standard set by WHO. The chronic exposure to arsenic in drinking water through over 4 million tubewells and foods grown in heavily arsenic contaminated soil is causing wide spread health hazards in our country. Arsenic is deposited in tissues and causes oxidative stress to cells resulting in multiple organ dysfunctions. This may lead to hundreds of thousands of death– a national catastrophe. Researches, trails, discussions, and seminars are going on to evolve ways to detoxify arsenic from the body by immediate biotransformation of inorganic arsenic, with rapid elimination from the body by any drugs, chemicals and nutrients that have strong anti-oxidative properties. National strategic planning should be adopted to prevent this catastrophe.

With the advancement of medical science and technology an effective sophisticated method is now available to treat problematic ulcers like Diabetic ulcers, Venous leg ulcers, Pressure sores, Burns etc with "Bioengeered Skin", a dermal component (like tiles of building) which is composed of living keratocytes and dermal fibroblast derived from neonatal foreskin. This "Bioengeered Skin" lacks many cellular component of skin, including melanocytes, endothelial cells and Langerhans cells, the absence of which may be advantageous, with own matrix proteins, growth factors and cytokines. Dematologists in our country may be encouraged to apply this modern technical know-how for better management of their patients.

Anthrax is an acute infectious disease caused by *Bacillus Anthrasis* with global distribution, more prevalent in developing countries with poor veterinary health care. Spores of this organism may remain alive for one year in contaminated soil and anthrax toxin is a thermolabile protein. Approximately 90% of human cases of anthrax are in cutaneous form and 5% is inhalation form. Gastrointestinal form is rare. Of these, inhalation type is dangerous with acute emergency and death sometimes occurs within hours. This is now a re-emerging infection which demands curative as well as preventive measures.

We express our determination to serve the healthcare professionals with our continued endeavour to satisfy their future needs. We would always value your views and suggestions.

May The Almighty bless you in the spirit of good health and professional success.



Dr. ATM Azizur Rahman
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Chronic Arsenic Toxicity Through Contaminated Drinking Water in Bangladesh: Magnitude of the Problem, Health Effects and Detoxification

G. H. Rabbani[1], Shyamal Kumar Saha[2]

INTRODUCTION

Various concentrations of arsenic in drinking water and soil are found in many countries in the world including developed and developing countries. The source of this arsenic in drinking water is the earth's crust where arsenic occurs widely. The arsenic contamination of drinking water may also be due to industrial pollution. In Bangladesh, the arsenic concentration in drinking water is alarmingly higher than the standard set by WHO. Together with the poor socio-economic and nutritional status of the population, the chronic exposure to arsenic in drinking water is causing widespread health hazards in Bangladesh.

Drinking water normally contains inorganic arsenic as arsenate (As(V)) and arsenite (As(III)). Inorganic arsenic is more dangerous than many other toxic substances. It is four times as toxic as mercury. Anyone who drinks arsenic in water at 60 parts per million (ppm) will soon die. But, organic arsenic in food is less toxic than inorganic arsenic. Most of the ingested arsenic is excreted from the body through urine, stool, skin, hair, and nail. Nonetheless, if the ingestion of arsenic through drinking water is very high, as in Bangladesh, our body normally cannot escape its toxic effects. Arsenic is deposited in tissues and causes oxidative stress to cells resulting in multiple organ dysfunctions.

A recent article in The New York Times on 10 November 1998 observes: "...Bangladesh is in the midst of a mass poisoning in history, dangerous levels of arsenic have been found in the ground water, entering millions of people, sip by sip as they drink from over 4 million tube wells." The report says "...if this were the United States, they'd call out National Guards and get everyone bottled water", "...arsenic in drinking water poses the highest cancer risk ever found, ...we could be talking about hundreds of thousands of deaths - this is really a medical emergency."

The problem is new to Bangladesh, and little is known about the health effects and pathogenesis of chronic arsenic poisoning through contaminated drinking water. We still do not know how we can remove arsenic contamination from our ground water nor do we know the effective treatment to detoxify arsenicosis patients.

GENESIS OF THE PROBLEM

About 3.5 to 4 million tube-wells (hand pumps) were installed in 1960s, all over the country by the aid agencies (mainly UNICEF) and the Government of Bangladesh to provide her 120 million people with safe drinking water at a minimum cost. Again, after liberation of Bangladesh, shallow tube well water was heavily promoted and developed as a safe and environmentally acceptable alternative to microbiologically unsafe untreated surface water. Although the tube well programmed significantly reduced the burden of diarrhoeal diseases and saved millions of lives, it has now turned into a major cause of tragedy.

In the 1980s, scientists began finding evidence of arsenic contamination, but only very recently (mid-1990s) has the crisis emerged into broad public awareness. The origin of the arsenic pollution is geological in this case - the arsenic is released to groundwater under naturally occurring aquifer conditions. Aquifers less than 300 m deep (mostly <100 m) provide Bangladesh with more than 90% of its drinking water. Another contributing factor for arsenic pollution appears to be the unrestricted use of underground water for agriculture. Withdrawal of large volume of underground water, often with insufficient recharge, led to a sharp fall in water table, causing aeration of the underground water and chemical contamination.

In the adjoining Indian state of West Bengal, ground water contamination by arsenic has been known for several years, and a likelihood of similar condition in the adjacent western Bangladesh had been predicted by the Indian scientists several years ago. However, it was not until June 1996, when arsenic poisoning was first detected in a few Bangladeshi patients presenting with skin changes in a northwest town bordering India[1]. Later, laboratory investigations confirmed the diagnosis of chronic arsenicosis, showing more than normal arsenic contents in the hair, nail, skin, and urine samples of 96 patients. A higher than normal content of arsenic (Bangladesh standard 0.05 mg/L, i.e., 50 ppb) was also found in 66% of the water samples taken from the shallow tube wells in that area.

Further studies carried out by the Dhaka Community Hospital, in collaboration with the School of Environmental Studies in Calcutta detected high arsenic content in the tube well water wherever it has been looked for. About 60% to 90% of the tube wells providing 97% of the country's drinking water supply were found to contain unacceptable levels of arsenic (0.05 to 3.0 mg/L), whereas the World Health Organization's safety standard for arsenic is 0.01 mg/L. Early observations by other organizations, including the government's public health department, NGOs and international aid agencies (UNICEF, World Bank) also indicated an alarming rate of arsenic contamination of the tube well water and prevalence of arsenic affected patients throughout the country.

THE MAGNITUDE OF THE PROBLEM

Many sporadic reports of arsenic contamination of tube well water and of poisoning cases that had appeared in the local press and newsletters are summarized in the Table. It is

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observed that by early 1998, a total of 8,065 tube-well water samples from 60 out of the 64 districts of the country were tested for the presence of arsenic by using field test kits and atomic absorption spectrophotometer. In 41 districts, the arsenic contents exceeded 0.05 mg/L, the maximum permissible limits recommended by Bangladesh standard, thus exposing 76.9 million people in these districts to the risk of arsenic poisoning[2]. However, according to various estimates reported to the press, the actual proportion of the population exposed to the risk may be more. Up till now, four people were reported to have died of arsenic poisoning[3]; however, there may be more deaths that were not reported.

Tube well water samples from Dhaka district and nine elevated districts in the northern Bangladesh, including the hill districts in Chittagong, were found to contain arsenic in the permissible range (0.01-0.05 mg/L). The reasons for this difference have not yet been found out. The distribution of arsenic contaminated tube wells in different districts of Bangladesh is shown in the map (Figure 1).

Districts affected	17	1	20	21	64	1	34	60	1
Tube wells tested	-	279	30,757	32651	19,000	13,043	3,106	8,065	438
% tube wells arsenic contaminated (0.05 mg/L)	-	91	10-60	60.6	21	98	38	51	97
Population exposed to the risk of poisoning	-	4,841	21 million	2,72,605	-	-	36 million	100 million	-
Population with skin lesion	680 (2 died)	330	831	1,802	2,400	15,000	228	-	-
Arsenic content in tube well water (mg/L)	0.05-0.08	-	-	-	-	-	-	-	-
Arsenic in hair (% having more than normal values)	-	334 (85)	-	-	2,342 (89)	-	228 (92)	2,167 (97)	400 (100)
Arsenic in nail	-	334 (96)	-	-	2,346 (89)	-	228 (98)	2,165 (94)	400 (100)
Arsenic in skin	-	-	-	-	-	-	-	200 (94)	11 (100)
Arsenic in urine	-	334 (97)	-	-	-	-	228 (85)	830 (94)	250 (100)
Sources*	1	2	3	4	5	6	7	8	9

1. The New Nation, 11 September,1996
2. DCH Newsletter, vol 8, 1997
3. The Daily Star, 14 December, 1998
4. The Daily Ittefaque, 3 January, 1999
5. The Daily Star, 11 December, 1998
6. The Daily Star, 12 December, 1998
7. See ref. 5 in the text
8. See ref. 6 in the text
9. Dhar RK et al. Dhaka Com Hos. Intl. Confc. On Arsenic Pollution, Dhaka, 1998, p51.

Table . Estimates of arsenic contaminated tube wells and arsenic-affected population in Bangladesh.

Figure 1. Arsenic contamination in groundwater of Bangladesh. From: Arsenic in groundwater: testing pollution mechanisms for sedimentary aquifers in Bangladesh. J.M. McArthur, P. Ravenscroft, S. Safiullah and M.F. Thirlwall. Water Resources Research, in press. © J.M. McArthur. "Analyses based on 18,417 (4,125 lab) aggregated by union. The surface estimated based on the union-wise probability assigned to the centroid of each union. Calculation by IDW using a fixed radius of 7.5 km, a 1.5 km grid, and 3.125 union data points."

A case study by Dhar et al.[4] of the Samata village in Jessore district illustrates the scenario of arsenic poisoning in Bangladesh. The total area of the village is 3.2 sq km with 4,841 people and 279 tube wells. It has been found that water of only 5 (2%) tube wells was safe for drinking (arsenic content <0.01 mg/L), 18 tube wells were moderately safe (arsenic content <0.05 mg/L), and 90% tube well water was unacceptable for drinking by the Bangladesh standard. Three hundred thirty people, including 27 children aged less than 12 years were identified as having arsenical skin lesions (mostly melanosis, leukomelanosis, and keratosis); arsenic content in urine, hair, and nail samples of these patients exceeded the normal limit in 97%, 85%, and 96% cases, respectively.

A recent case-controlled study by Rahman et al.[5] showed that the long-term exposure to arsenic through drinking of arsenic contaminated water was associated with high prevalence of diabetes mellitus among the Bangladeshi population. The same group of authors[6] have also assessed the risk of hypertension in a group of Bangladeshi adults exposed to high level of arsenic in drinking water and found a significant correlation between arsenic ingestion and hypertension.

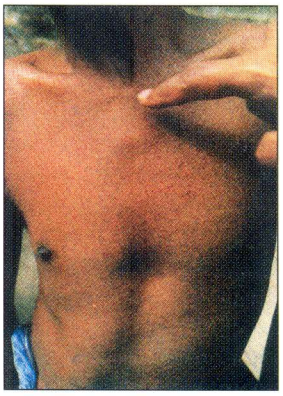
Long-term epidemiological studies to determine the biomedical and environmental characteristics of arsenic poisoning with regard to age, gender, time, and place have not yet been undertaken, and the related risk factors have not been identified.

CLINICAL PRESENTATION AND RISK TO HUMAN HEALTH

The health effects of chronic human exposure to non-overtly toxic doses of arsenic in drinking water and food can be broadly divided into noncancer effects and cancer effects. Chronic exposure to arsenic causes its toxic effects to all organs and cells

of the body. It interferes with the action of enzymes, essential cations and transcriptional events ensuing a multitude of multisystemic noncancer effects. Chronic arsenic exposure may cause hyperpigmentation and keratosis leading to skin cancer, gastrointestinal disturbances ranging from mild abdominal cramping and diarrhea to severe life-threatening gastrointestinal hemorrhage secondary to esophageal varices, hepatocellular necrosis, insidious development of peripheral vascular disease leading to gangrene of the extremities, hypertension and ischemic heart disease, hematological abnormalities, obstructive and restrictive pulmonary diseases, generalized immunosuppression, peripheral neuropathy, and metabolic disorders including diabetes[7]. In recent times, an increase in the prevalence of some diseases in Bangladesh such as diabetes may be explained by the chronic exposure to arsenic.

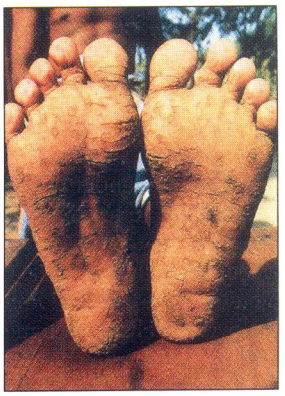
In a study[8], arsenic-affected population in southwestern district (Jessore) in Bangladesh and in the neighboring Indian state of West Bengal, it is reported that the usual clinical manifestations are diffused and spotted melanosis, diffused and spotted keratosis, and non-pitting edema; the common symptoms are bronchial problems and burning sensation of the skin. Khan et al.[9] reviewed the clinical data from Bangladeshi arsenic-affected patients and reported that the most common clinical manifestations are melanosis (87.4%), keratosis (67.7%), leukomelanosis (35.5%), and hyperkeratosis (38.7%). Other findings are conjunctivitis (6.3%), bronchitis (10.5%), and hepatomegaly (2.2%).



Recently, in an ongoing study, we have documented typical skin changes (photographs) including other systemic involvement in patients in the study area of Hajiganj, Chandpur. We have observed typical skin changes including plantar and palmer keratosis, gastrointestinal symptoms, anaemia, signs of liver disease, and peripheral neuropathy. Chronic arsenic toxicity is already known to cause liver damage[10]. Guha et al.[11] have recently described 13 Indian patients who have developed hepatomegaly and non-cirrhotic portal fibrosis associated with arsenical dermatosis due to prolonged exposure to arsenic (0.2 - 2 mg/L) through drinking water. Although similar findings have not yet been reported from Bangladesh (due to lack of studies), the risk of liver involvement cannot be excluded because of the similarity of biological and environmental characteristics between these two populations.

It has been observed that skin manifestations of arsenic toxicity develop slowly, usually over three to six months depending on the dose and duration of the toxic material, and age and nutritional status of the exposed individual[12,13,14]. The arsenic contents of 90% of tube well water in our study site at Hajiganj, Chandpur as well those reported by Biswas et al.[8] from Jessore district were more than the maximum permissible limit by the Bangladesh standard (>0.05 mg/L). The lowest arsenic concentration in water producing dermatosis was found to be 0.02 mg/L[13].

Arsenic is an important cause of skin cancer, and the high incidence of keratosis, hyperkeratosis, and skin cancer has been associated with drinking water containing more than 0.3 to 0.5 mg/L of arsenic[15,16]. Most authorities believe that ingestion of approximately 1 mg/L of arsenic per day in drinking water may give rise to skin changes within a few years[8].



PATHOGENESIS OF ARSENIC POISONING

The inorganic arsenic is absorbed more readily than the organic forms because of its high lipid solubility. Once arsenic is within the body, it binds to hemoglobin, low molecular weight plasma proteins, and leukocytes and is redistributed to the liver, kidney, lung, spleen, and intestines. Over a period of weeks, manifestations may be found in skin, hair, nails, bone, muscle, and even nervous tissue. As mentioned above, chronic exposure to arsenic causes carcinogenesis and other non-carcinogenic diseases. There are a number of possible modes of action of arsenic carcinogenesis: chromosomal abnormalities, oxidative stress, altered DNA repair, altered DNA methylation patterns, altered growth factors, enhanced cell proliferation, promotion/progression, gene amplification, and suppression of p53. In vitro studies of human and animal cells show that genotoxic effects occur at submicromolar concentrations of arsenide that are similar to those found in urine of humans consuming drinking water[17,18]. Arsenic poisoning has inhibitory effects on mitochondrial respiratory function by inhibiting the pyruvate dehydrogenase complex (Figure 2). Inhibition of mitochondrial respiration results in decreased cellular production of ATP and increased production of hydrogen peroxide. These effects cause formation of reactive oxygen species, resulting in oxidative stress. There is evidence that intracellular production of reactive oxygen species inhibits the heme biosynthetic pathway. It is known that oxidative stress is a cause of DNA damage. It is likely that oxidative stress induced by chronic exposure to arsenic also mediate DNA

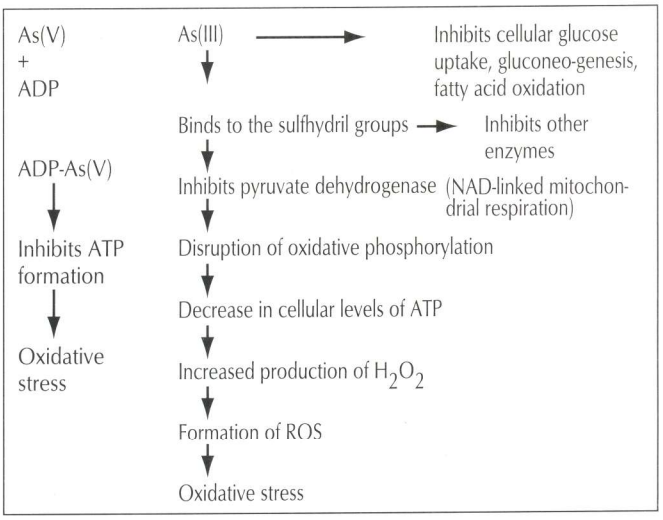


Figure 2. Mechanisms of arsenic toxicity. As(V) competes with inorganic phosphate for ADP. Therefore, ADP-As(V) is formed, inhibiting formation of ATP from ADP. Ultimately, this causes oxidative stress. As(V) is biotransformed to As(III). As(III) inhibits cellular enzymes, especially binding to the sulphydryl groups ultimately causing oxidative stress. It also inhibits cellular glucose uptake, gluconeogenesis and fatty acid oxidation.

damage. The intracellular production of reactive oxygen species might play an initiating role in the carcinogenic process by producing DNA damage[17].

By using human-hamster hybrid cells, Liu et al. have shown arsenide induces a dose-dependent increase in intracellular oxyradical production[18]. Concurrent treatment of cells with arsenide and the radical scavenger dimethyl sulphoxide (DMSO) reduced the oxyradical concentration to control levels. This provides that reactive oxygen species, particularly hydroxyl radicals, play an important causal role in the genotoxicity of arsenical compounds in mammalian cells. Barchowsky A et al. measured the reactive species generated in cultured porcine vascular endothelial cells exposed to levels of arsenide that initiate cell signaling[19]. They found that superoxide and H_2O_2 are the predominant reactive species produced by endothelial cells after arsenide exposures that stimulate cell signaling and activate transcription factors. Flora SJ provides in vivo evidence of arsenic-induced oxidative stress in liver, brain and RBC[20]. He reports that twelve weeks of arsenic (12 mg/kg) exposure was found to deplete glutathione (GSH) levels, increase oxidized glutathione (GSSG) and promote malondialdehyde (MDA) production in both liver, brain and RBC samples suggesting arsenic-induced oxidative stress. In order to assess possible risk to brain function by drinking arsenic contaminated water, in a study, rats were given arsenic mixed in drinking water for 40 days. There was increased lipid peroxidation at all doses of arsenic, including the 'permissible limit', decrease in glutathione level, superoxide dismutase and glutathione reductase activities, indicating the free-radical-mediated degeneration of brain[21]. In a study, we administered arsenic trioxide to rabbits for one week and found that it causes a decrease in the concentration of whole blood GSH and an increase in the serum level of thiobarbituric acid reacting substances (TBARS, index of oxidative injury) as compared to the normal (basal) levels (Figure 3 and Figure 4). Together, it appears that free radical injury to the body is an important cause of pathological and clinical features of chronic arsenic toxicity.

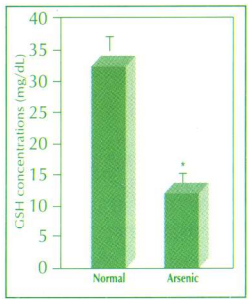


*Figure 3. Arsenic-induced depletion of whole blood GSH. A group of 8 rabbits were treated with arsenic trioxide at a dose of 4 mg/kg/day, single dose, for 7 days. *p<0.0001 vs. normal.*

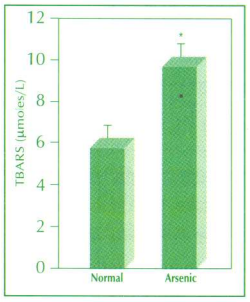


*Figure 4. Arsenic-induced increase in serum TBARS concentration. A group of 8 rabbits were treated with arsenic trioxide at a dose of 5 mg/kg/day, single dose, for 7 days. *p=0.01 vs. normal (basal).*

BIOTRANSFORMATION, DETOXIFICATION, AND DISPOSITION OF INGESTED ARSENIC

Inorganic arsenic is readily absorbed from the gastrointestinal tract. Arsenic appears to be poorly absorbed through intact human skin but can bind externally to skin and hair from contaminated water and soil. After absorption, inorganic arsenic is rapidly reduced, mainly in blood, and methylated in liver to produce less toxic metabolite.

Inorganic arsenic is methylated to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) (Figure 5). These metabolite are less reactive with tissue constituents, less acutely toxic, less cytotoxic, and more readily excreted in the urine[22,28]. If the methylation reactions are inhibited, the tissue concentration of arsenic is increased[29].

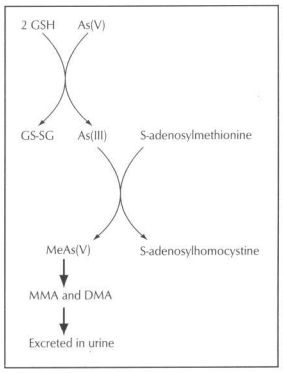


Figure 5. Biotransformation of inorganic arsenic to less toxic metabolites. GSH, reduced glutathione; GS-SG, oxidized glutathione; MeAs(V), methylated arsenic V; As(V), arsenic V species; As(III), arsenic III species.

In methylation reactions, glutathione (GSH) acts as a reducing agent for As(V) species, and the resulting As(III) species can then accept a methyl group from S-adenosylmethionine (SAM) to produce methylarsenic (V) (MeAs(V)) species in an oxidative-addition reaction[30,31] (Figure 6). The MMA and DMA are the major end products in mammals. MMA and DMA are excreted in the urine faster than the inorganic arsenic.

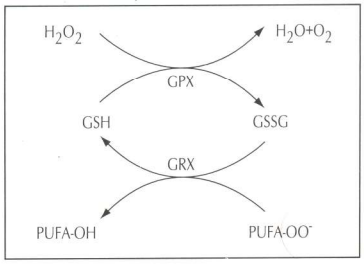


Figure 6. Glutathione (GSH) antioxidative pathways. GSH converts H2O2 into H2O and O2, and selenium dependent glutathione peroxidase (GPX) converts GSH to GSSG at the expense of H2O2. The oxidized GSH (GSSG) is reduced back to GSH by glutathione reductase (GRX) and at the same time metabolizes lipid peroxy radicals (PUFA-OO·) into the hydroxy fatty acids (PUFA-OH).

THERAPEUTIC GOAL

From the mechanism of biotransformation of inorganic arsenic (Figure 5), it is clear that GSH plays a crucial role in detoxifying and eliminating arsenic from the body. GSH is also necessary to neutralize free radicals produced during arsenic toxicity, in chronic or acute poisoning (Figure 6).

But we find from our results (Figure 3 and Figure 4) and form published reports that arsenic poisoning (chronic or acute) causes an increase in TBARS and a depletion of GSH levels. This means that chronic arsenic poisoning not only causes injury to cells, also depletes the body's defense system, ultimately aggravating the clinico-pathological condition. So, in any medical therapy, we must target to transform toxic forms of arsenic to non-toxic forms, inhibit free radical injury, help repair the injury already done and maintain a robust antioxidative defense system. An ideal anti-arsenicosis drug should fulfill all these criteria.

The treatment goal of the poisoning due to chronic exposure to arsenic is to eliminate the poison (arsenic) from the environment, to neutralize the poison in the body or eliminate it from the body, to reduce the toxic effects and repair the damage to organs and cells. Rapid elimination of the poison from the environment is certainly a difficult task if we consider the huge strategic planning and cost. Therefore, we need to rapidly detoxify the poison in our body before it can cause any toxic effects.

Now, the question is how we can target to detoxify arsenic once inside the body. Detoxification can be enhanced by immediate biotransformation of inorganic arsenic to less toxic organic arsenic, by rapid elimination of arsenic from the body and preventing tissue deposition and by increasing the ability of

body's antioxidative defense system. Detoxification can be done by chelation of arsenic. One such chelating agent is dimercaptosuccinic acid, but even this best chelating agent for arsenic is reported to show no encouraging benefits compared with placebo in a recent study[32]. Furthermore, dimercaptosuccinic acid has many adverse effects as well as it is very costly.

Therefore, any drugs, chemicals, and nutrients that have strong antioxidative properties could be effective in reducing the arsenic toxicity in the body. It is necessary to emphasize that the supplementation of antioxidant must be sufficient to neutralize the toxicity and to build up antioxidative system. So, new agents with strong antioxidative properties need to be explored. Dose of the known antioxidant need to be evaluated to match the level of toxicity in Bangladeshi patients. Efficiency of combination of various antioxidant needs to be evaluated to effectively neutralize the arsenic toxicity. Recently, we have made some progress in this area of research and hope to communicate in the near future.

CONCLUSION

An environmental health disaster is unfolding in Bangladesh and neighboring countries due to a high concentration of arsenic in drinking water and in soil. Tens of millions of people in many districts are drinking ground water with arsenic concentrations far above acceptable levels. The ground water contains more than 0.05 mg/L (50 ppb) of arsenic. Thousands of people have already been diagnosed with poisoning symptoms, even though much of the at-risk population has not yet been assessed for arsenic-related health problems. Basic research in the area of arsenic toxicity, its mechanisms and pathogenesis should be given priority so the evolving knowledge can be used to identify an ideal medical therapy for chronic arsenic toxicity. Considering the huge strategic planning necessary for the elimination of arsenic from the environment and the fact that we can hardly avoid health hazards related to arsenic in an environment where we are constantly exposed to some degree of arsenic contamination not only in drinking water, but also in foods grown in heavily arsenic contaminated soil, we must find an ideal agent to detoxify ingested arsenic before it can cause any injury to the body.

Acknowledgement Ms. Mastura Akhtar, MSc, Senior Research Assistant and Ms. Farzana Marni, MSc, Research Assistant, assisted in the experiments summarized in Figure 3 and Figure 4.

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Bioengineered Skin

Jasmin Manzoor

INTRODUCTION

In this era of advancement of Medical Science and Technology, development in effective and modern management in dermatological problems mostly chronic ulcers like Diabetic ulcers, Venous pressure ulcers, Burns, pressure sores etc is with significant progress. Dermatologist as well as their patients are facing difficulties to manage these ulcers with increasing socioeconomic burdens. To treat these ulcers Medical Scientist developed "Bioengineered Skin" with modern know-how and facilities. Many products have been developed under the category of "bioengineered skin" is reportedly the most advanced organ system developed in the laboratory, at least in terms of its structural complexity and potential to stimulate living skin.[1,2] The most extensive clinical experience in the United States and Canada is with a bilayered skin construct called Apligraf®.

Although the technology for developing bioengineered skin is highly sophisticated, the product is relatively easy to use, does not need hospitalization.

In this article I shall highlight compositions, properties, applications and technical features of "bioengineered skin".

A HISTORY OF BIOENGINEERED SKIN

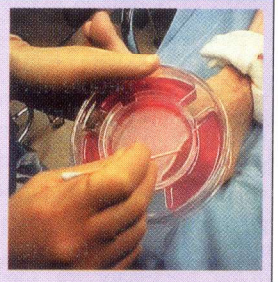
For several decades, medical researchers sought effective methods to grow or create sheets of natural or synthetic human skin to treat severe burns, venous insufficiency, and other skin injuries. For many years, researcher focused on growing cellular components of the skin, such as fibroblasts and keratinocytes, which were cultured and propagated in vitro. Eventually, starting from small skin biopsies, researcher grew sheets of keratinocytes for the treatment of burns and chronic wounds.

BIOENGINEERED SKIN AT A GALANCE

SIZE : 7.5 cm diameter
COST: $975
DURATION OF PROCEDURE: 30-40 minutes

APPLICATION PROCESS:

- Surgical debridement-if necessary, preferably a few days before graft application
- Remove graft from its packaging, moisten with saline
- Meshing or fenestrating is Performed as needed
- Place graft over the wound, allowing a 1-1.5cm overlap over the margins
- Suture only when needed
- Dress with Xeroform, foam dressing, an additional layer of Xeroform, and gauze
- Wait six weeks before considering additional application



Bioengineered Skin being removed form its packaging unit. The white layer being teased away from the edge of the insert with a cotton applicator is Bioengineered Skin. The pink material around the insert is a gel-like material which provides nutrients to graft and keeps it alive.

At first, researcher thought that keratinocytes kept in culture lost immunologic properties, thereby decreasing clinical rejection.[3] However, at least for some types of chronic wounds, they later found that cultured cells stimulated the wound to heal from the edges. This observation suggests that cells transplanted into a wound act more as a stimulus for wound repair than as an actual replacement. Bioengineered skin may work this way as well, although the data are not yet available on its mechanism of the action and the length of time its allogenic cells remain in the wound.

Keratinocyte sheets have now been used for more than a decade in the treatment of burns and chronic wounds. The problem is the keratinocyte sheets are very much a "laboratory product." They are difficult to handle, fall apart if not held on backing material, and have no resilience and durability. Therefore, a dermal component, either by itself or to support the keratinocyte sheet, was highly desirable, especially since dermal components and dermal cells could add to the efficacy of cultured skin.

INDICATION

Chronic wounds: Venous leg ulcers.
Diabetic ulcers
Pressure sores

Skin surgery

Burns

DEVELOPMENT OF BILAYERED LIVING SKIN AND HOW IT WORKS

Though many products have been developed under the category of "bioengineered skin." This graft is reportedly the most advanced organ system developed in the laboratory, at least in terms of its structural complexity and potential to stimulate living skin.[1,2] It is composed of living keratinocytes and dermal fibroblasts derived from neonatal foreskin and propagated in culture. A wide variety of safeguards are in place to ensure the absence of infectious agents in the donor cells. The manufacturing process of this graft has been reviewed extensively.[1] In simple terms, a gel of dermal fibroblasts and type 1 bovine collagen is formed. After it contracts, the gel is overlaid with neonatal keratinocytes to form a bilayred construct. Epidermal differentiation and the formation of a stratum corneum occur when the epidermal component of the bilayred skin construct is exposed to air. This graft looks like human skin, and is alive.[1,2] It makes its own matrix proteins, growth factors

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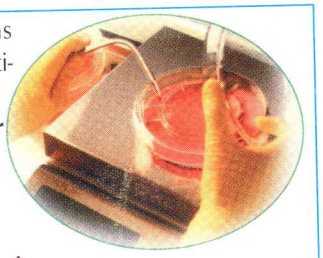
Bioengineered skin contains living human epidermal keratinocytes and dermal fibroblasts.

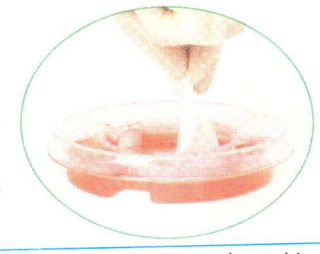


Formation of the Dermal Layer

* Fibroblasts are seeded on a semipermeable membrane with bovine type I collagen
* Fibroblasts divide, multiply, and contract the collagen filaments
* Dermal matrix forms and condenses

Formation of the Epidermis

* Kerationcytes are seeded into the dermal matrix
* Keratinocytes proliferate and differentiate
* Epidermal layer is then exposed to air promote cornification



The results is Bioengineered Skin the only bilayered living skin construct.

(ECGF, FGF, IGF, IL, PDGF, TGF, TNF, and VEGF) and cytokines found in human skin.[5,6] If wounded, it can heal by itself. It lacks, however, many cellular components of skin, including melanocytes, endothelial cells, and Langerhans cells, the absence of which may be advantageous. Since endothelial cells and langerhans cells are professional antigen presenting cells, their absence may explain the lack of clinical rejection observed using this graft. The absence of melanocytes reduces theoretical concerns associated with possible transformation of these cells in culture. Eventually, the patient's own melanocytes seems to migrate into the healed wound after treatment, just as when chronic wounds heal by themselves. Therefore, do not think of this graft as "white skin," but rather as a "generic skin." It can be used effectively in patients with dark skin color.

Each unit of graft is supplied to physicians and hospitals in a sealed and sterile plastic container. Inside the plastic bag, the graft sits in a plastic insert, over a bed of red agar-like material. The material contains nutrient required for this bioengineered skin product to remain alive. Each unit of graft measures 7.5cm in diameter. At $975 per application, graft represents a cost effective measure as compared to long term treatment for chronic ulcers. Upon its arrival, the unit is to be placed in a small tabletop incubator . Its shelf life is five days, requiring physicians to schedule patients according to that time-frame. In our experience, this has not been a problem, but there are serious efforts under way to extend the product's shelf life. People often ask how this graft compares with autologous split thickness grafts. There are no studies to answer that question. Remember that graft is composed of young newborn cells, and that these cells are generally more proliferative and have increased ability to synthesize extracellular matrix components. Therefore, this graft offers the potential to deliver young, healthy cells to an old wound. This stimulation to heal ulcers begins about six to eight weeks after treatment with this graft and continues for at least 24 weeks. Single application is usually enough to "jump start" the healing process.

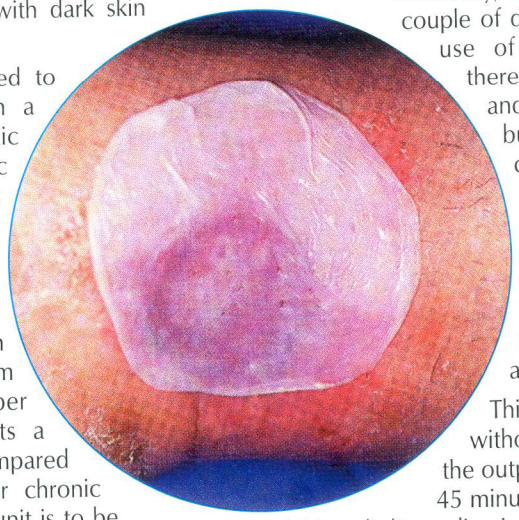
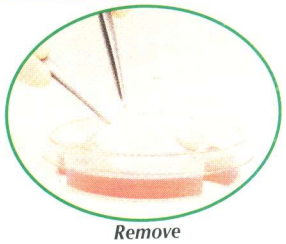


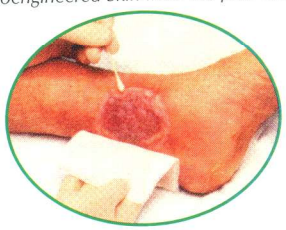
Fig. Bioengineered Skin applied to a venous ulcer. Cuts on the surface of graft allow fluid to escape and not accumulate under the product.

APPLYING THE GRAFT

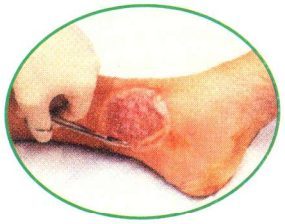
Before applying the graft, debride wound of fibrotic and necrotic material to enhance adherence. This graft should not be used on infected wounds or on patients with known hypersensitivities to any components of this bio-engineered graft. If surgical debridement becomes necessary, we perform it a couple of days before the use of this graft. If there is no cellulitis and the bacterial burden is under control, systemic factors have been corrected to the extent possible, presumably, the ulcer is now ready for graft application.



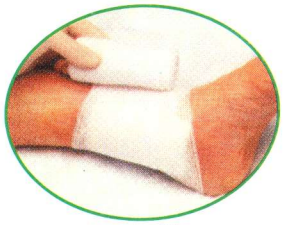
Remove
Bioengineered Skin from the petri dish.



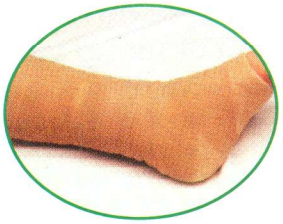
Apply
the product to the prepared wound bed immediately after removing from packaging.



Position
the product within the wound bed and trim wit sterile scissors to match the contours of the wound.

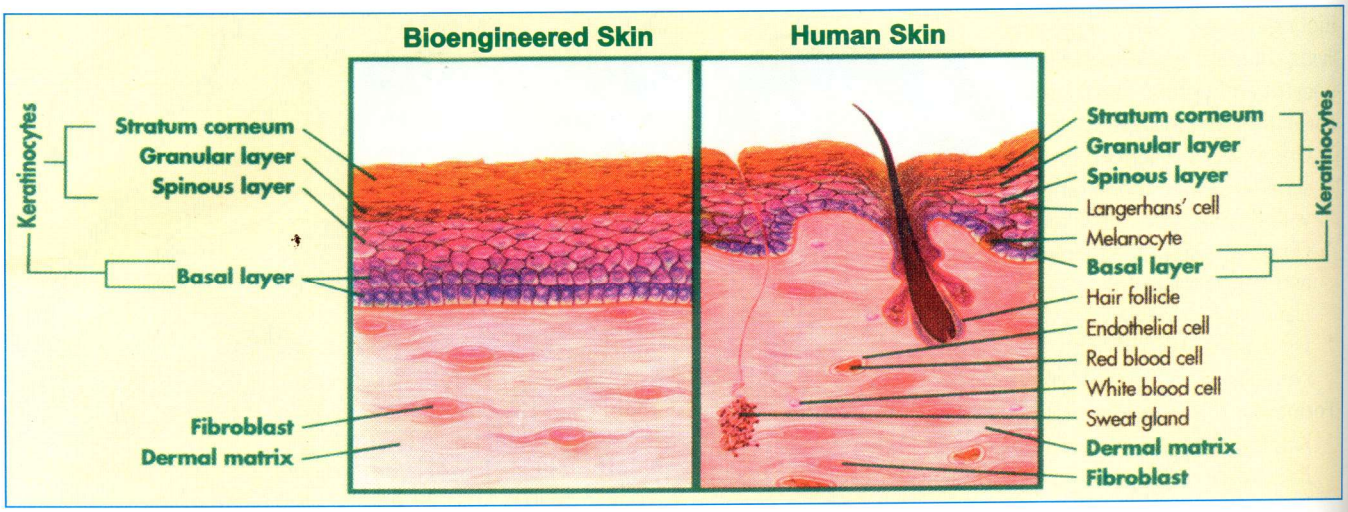


Immobilize
and anchor GRAFT with a nonadherent primary dressing, bolster, and elastic compression wrap.

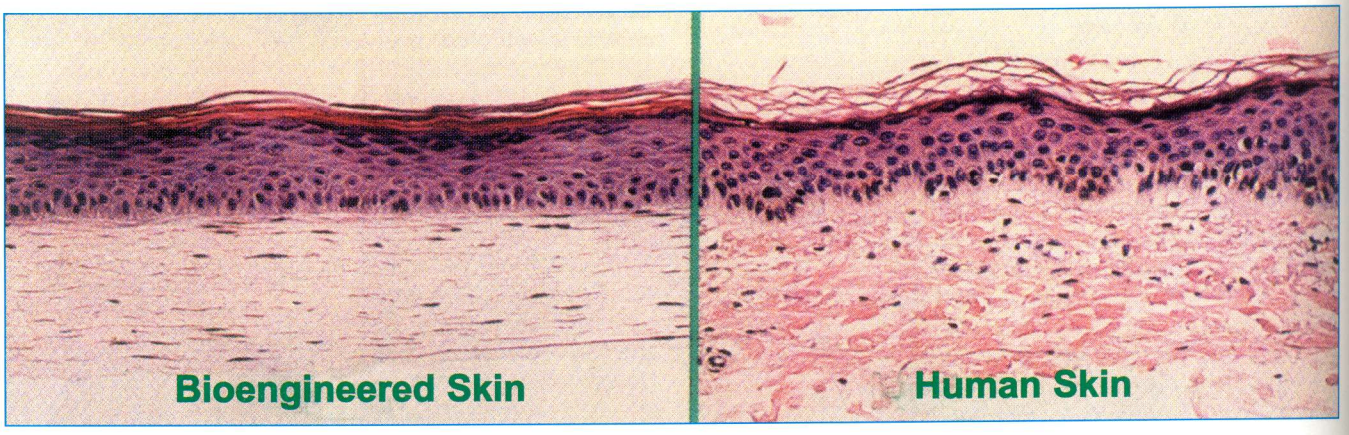


Determine
the appropriate follow-up for the patient.

This graft is generally applied in the outpatient setting without the need for a doner site. The patient comes to the outpatient department and goes home after about 30 to 45 minutes. The ulcer bed is irrigated extensively with sterile saline immediately before the procedure, and the sealed bag containing graft is then taken from the incubator. We pour a small amount of saline on top of the graft to keep it moist and then, using the wooden end of a cotton applicator, gently tease the graft from the petri dish. Apply the product to



Cross-Sectional Illustration:
Bold-faced items are contained in Bioengineered skin and human skin.



Hematoxylin-Eosin Stained Photomicrographs

the prepared wound bed immediately after removing from packaging. Position the product within the wound bed and trim with sterile scissors to match the contours of the wound. Immobilize and anchor the graft with a nonadherent primary dressing, bolster, and elastic compression wrap. Determine the appropriate follow-up for the patient.

EFFICACY OF THE BIO ENGINEERED GRAFT

It is unclear why this graft is most effective in difficult to treat ulcers. We hypothesize that cells present in chronic wounds are altered by pathogenic mechanisms and become unresponsive to certain growth factors. This graft can deliver "new cells" which may, at least for a period of time, provide the right matrix materials and growth factors "conditioning" the wound and stimulating healing. This graft is therefore able to adjust to the wound micro-environment.

CONCLUSION

Thanks to recent advances in cell and tissue culture techniques and researchers who have been abled to "bioengineer" human skin equivalents. Bioengineered skin will redefine the way we treat wounds- especially ulcers caused by venous insufficiency. Time and additional trials will test the effectiveness of this graft in other clinical situations. While this graft is exciting, we must not forget that proper wound care remains critical to the overall clinical outcome. Learning how to use this graft now will increase your ability to serve your patient's needs.

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Bacillus Anthrax---- Re-Emerging Issue

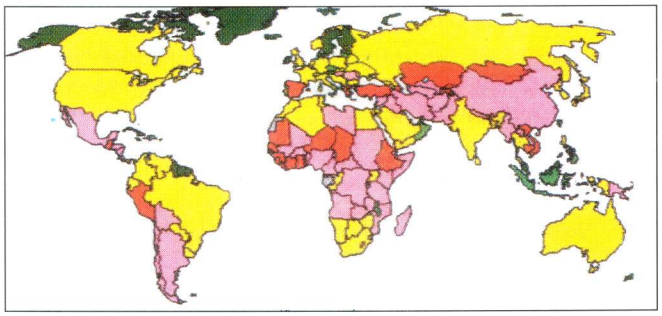
M A Kashem Khandaker[1], Shohael Mahmud Arafat[2], Sk. M.A Jafar[3], Akhtarun Naher[4]

ANTHRAX

Anthrax is greek word for coal. This name is implied as it creates dark sores on the skin. Anthrax is an acute infectious disease caused by the spore forming organism *Bacillus anthracis*. This occurs commonly in herbivores like cattles, sheeps, goats, camels, antilopoes and other herbivores. Humans become infected when *B. anthracis* spores are introduced into the body by contact with infected animals or contaminated animal products, insect bites, ingestion or inhalation. Aerosolized spores of *B. anthracis* have the potential for use in biological warfare or bioterrorism.

EPIDEMIOLOGY

The distribution of anthrax is global with more prevalence



View as monochrome

Hyperendemic/epidemic
Endemic
Sporadic
Probably free
Free
Unknown

amongst the developing countries and countries with poor vatenrinary health care. Grazing animals become more infected when they forage for food in area contaminated with spores of *B. anthracis*. Anthrax in herbivores tends to be more severe with high mortality. Terminally ill animals with overwhelming infections often bleed from the nose, mouth and bowel, thereby contaminating soil or water with vegetative *B. anthracis* that can sporulate and persist in the environment. The carcasses of infected animals provide additional foci of contamination. Humans are more resistant to anthrax than animals. Human cases can be classified into two groups, agricultural and industrial cases. Agricultural cases result most often from contact with infected animal that have anthrax (e.g. during skinning, butchering or dissecting.), from bites of contaminated flies and in rare instances from ingestion of contaminated meat. Industrial cases obtain infection from exposure to contaminated hides, goat hair, wool or bones.

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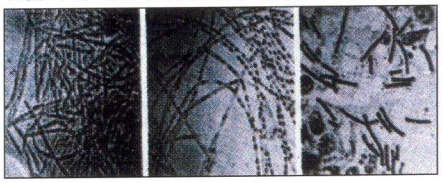
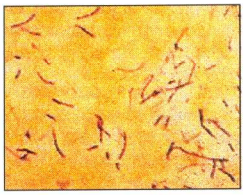
BACTERIOLOGY

The anthrax bacillus was the first bacterium shown to be the cause of a disease. In1877, Robert koch grew the organism in pure culture, demonstrated its ability to form endospore and produced experimental anthrax by injecting into animals.



Robert Koch's original micrographs of the anthrax bacillus



Bacillus anthracis

Bacillus anthracis is a very large, gram positive, spore forming rod (1-1.5 µm-x 4-10µm). Genotypically and phenotypically, it is very similar to *Bacillus cereus* which is found in soil habitats around the world.

PATHOGENESIS

Bacillus anthracis is an extracellular pathogen that can evade phagocytosis, invade the blood stream, multiply rapidly to a high population density in vivo and kill quickly. Capsular polypeptide and anthrax toxin are the principal virulence factors of *B. anthracis*. It possesses a unique cell wall polypeptide antigen and forms a single antigenic type of capsule consisting of poly-D-glutamate polypeptide. All virulent strains of *B. anthracis* form this capsule. Smooth(S) to Rough (R) variants occur, which is correlated with the ability to produce the capsule. R variants are relatively avirulent.

This capsule is itself nontoxic but functions to protect the organism against bactericidal components of serum and phagocytes and against phagocytic engulfment. It plays the most important role at the establishment of the infection than the terminal phase which is mostly attributable to anthrax toxin.

In addition to the capsule, virulent strains of *Bacillus anthracis* produce three distinct antigenic components related to a complex exotoxin called the anthrax toxin. Each component of the toxin is a thermolabile protein with a molecular wt. of approximately 80 Kda.

a. Factor I is the edema factor [EF] which is necessary for the edema producing activity. EF is known to be an inherent adenylate cyclase.

b. Factor II is the protective antigen [PA] because it induces protective antitoxic antibodies. PA is the binding site of anthrax toxin which has to active domain of the anthrax

toxin which has two active domains EF [above] and LF [below].

c. Factor III is the lethal factor [LF] because it is essential for the lethal effects of the anthrax toxin.

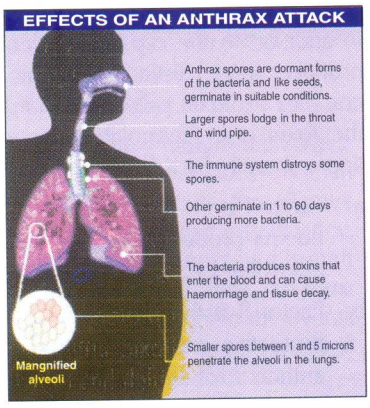
PA binds to plasma membranes of the target cells and is cleared by a cellular protease into two fragments. The larger fragment remains on the cell surface, displays a single binding site for a domain that is present in both FF and LF, and serves as a specific receptor that mediates endocytic entry of EF or LF into target cells. The activity of EF, a calmodulin dependent adenylate cyclase, is expressed within human or animal cells that provide both the calmodulin activator and the ATP substrate for EF. The biological functions of which includes formation of edema in anthrax lesions by the enzymatic action of EF. PA mediated entry of LF into susceptible cells leads to cell death by an unknown mechanism.

Cutaneous anthrax is usually acquired via injured skin and mucous membranes. A minor scratch or abrasion, usually on an exposed area of the face or neck or arms, is inoculated by spores from the contaminated soil, animal or carcass. The spores germinate, vegetative cells multiply and a characteristed gelatinous edema develops at the site. Histologically this lesion is characterized by necrosis, vascular congestion, hemorrhage and gelatinous edema. The number of leukocytes are disproportionately small in comparison with the tissue damage. The clinical description of malignant pustule is not in concordance with the pathologic finding. Inhalation anthrax. (Woolsorter's disease) results most commonly from inhalation of spore containing dust where animal hairs or hides are being handled. Macrophages ingest the spores, some of which undergo lysis and destruction. Surviving spores are transported via lymphatics to mediastinal lymphnodes, where germination may occur upto 60 days later. Once germination occurs disease manifests rapidly.Hemorrhagic necrosis of the nodes, in association with mediastinitis and overwhelming *B. anthracis* bacteremia, may develop rapidly.

Gastrointestinal anthrax develops from ingestion of undercooked meat from animals with anthrax. It will occur following deposition and subsequent germination of spores in upper or lower gastrointestinal tract. The former results in oropharyngeal form of disease and latter results in primary intestinal lesions occurring predominantly in terminal ileum or cecum. Intestinal lesions only occur by those organisms who can survive passage through stomach. Lesions in the throat and intestine are accompanied by hemorrhagic lymphadenitis.

B. anthracis bacteremia can develop in any form of anthrax and occurs in almost all fatal cases.

Meningitis due to *B. anthracis* is a very rare complication that may result from any primary infection.



CLINICAL FEATURES

Approximately 95 percent of human cases of anthrax are the cutaneous form and about 5 percent the inhalation form. Gastrointestinal anthrax is rare. Anthrax meningitis occurs in a small percentage of all cases and is a frequent complication of overwhelming *B. anthracis* bacteremia.

CUTANEOUS ANTHRAX

Areas of exposed skin, such as arms, hands, face and neck are the most frequently affected. Within days of inoculation of *B. anthracis* spore in the skin, a small red macule appears. During the next week, the lesion typically progresses through papular and vesicular or pustular stage to the formation of an ulcer with blackened necrotic painless, depressed eschar surrounded by a highly characteristic, expanding zone of brawny edema. The early lesion might be pruritic and the fully developed lesion is painless. Small satellite vesicles may surround the original lesion and painful nonspecific regional lymphadenits is common. Most patients are afebrile with mild or no constitutional symptoms. In severe cases however edema might be very extensive and associated with spontaneous healing will occur in 80-90% of cases, but edema may persist for several weeks. The eschar dries, loosens and fall off leaving no permanent scar. In 10-20% infections without treatment results in progressive infection, bacteremia develops and is often associated with high fever and rapid death.

INHALATION ANTHRAX

The frequent similarity of presentation of inhalation anthrax (woolsorter's disease) to those of severe viral respiratory diseases make the early diagnosis difficult and would require a high degree of suspicion. The clinical presentation has been described as two stage disease.

Patients first develop a spectrum of non specific symptoms, including fever, dyspnea, cough, headache, vomiting, chills weakness, abdominal pain and chest pain. This stage last from few hours to a few days. In some patients a brief period of recovery ensue other patients progress directly to the second stage.

The second stage develops abruptly with sudden fever, dyspnea, diaphoresis and shock. Massive lymphadenopathy and expansion of the mediastinum leads to stridor in some cases. A chest radiograph most often showed mediastinal widening. consistent with lymphadenopathy. Upto half of patients develop hemorrhagic meningitis, with concomitant meningismus, delerium and obtundation. In the second stage cyanosis and hypotension progress rapidly, death sometimes occur within hours.

GASTROINTESTINAL ANTHRAX

The presentation of gastrointestinal anthrax is variable. It presents initially with nausea, vomiting and malaise and progressing rapidly to bloody diarrhea, acute abdomen or sepsis. Massive ascites has occurred in some cases of gastrointestinal anthrax. Advanced infection may appear similar to the sepsis syndrome occurring in either inhalation or cutaneous anthrax.

The major features of oropharyngeal anthrax are fever, sore throat, dysphagia, painful regional lymphadenopathy and toxemia. Respiratory distress may be evident. The primary lesion is most often on the tonsils.

DIAGNOSIS

Presumptive identification in a hospital laboratory is based on the direct Gram's stained smear of a skin lesion (vesicular fluid or eschar), cerebrospinal fluid or blood showing encapsulated gram positive bacilli.

The most useful microbiological test is the standard blood culture which should show growth in 6 to 24 hours. It grows in sheep's blood agar cultures as non hemolytic colonies and large, nonmotile, noncapsulated, gram positive, spore forming rods. Growth doesn't occur in Mac-Conkey agar.

Confirmatory diagnostic tests are performed at a level of the Laboratory Response Network for Bioterrorism (LRN), where the growth of virulent strains on nutrient agar in the presence of 5% CO_2 produces heavily encapsulated bacilli that may be visualized with India-Ink staining. Additional criteria for the confirmation of the presence of *B. anthracis* include susceptibility to lysis by gamma-phage or direct fluroscent antibody staining of cell wall polyscaccharide antigen.

Serological test such as enzyme linked immunosorbent assay, for protective antigen and polymerase chain reaction are available at the national reference laboratories.

Patient with mild disease usually have normal leukocyte count but with severe infection has polymorphonuclear leukocytosis.

ANTI MICROBIAL THERAPY

Penicillin has been the drug of choice for anthrax for many decades and only rarely has penicillin resistance been found in naturally occurring isolates.

Table 1. Recommendations for Antimicrobial Therapy of Clinical Inhalational Anthrax.

Type of Therapy	Adults (Including Pregnant Women and the Immunocompromised)	Children
Initial Therapy	Ciprofloxacin, 400 mg IV every 12 hr	Ciprofloxacin, 20-30 mg/kg of body weight per day IV, divided into 2 daily doses
Optimal Therapy if strain has proved susceptible	Penicillin G, 4 million U IV every 4 hr or Doxycycline, 100 mg IV every 12 hr	Ciprofloxacin, 20-30 mg/kg per day IV, divided into 2 daily doses or Penicillin G, 50,000 U/kg IV every 6 hr children <12 yr old; 4 million U IV every 4 hr in children ≥ 12 yr old

In vitro *B. anthrax* has been found to be susceptible to many antimicrobials like ciprofloxacin, ofloxacin, levofloxacin, tetracyclines, chloramphenicol, macrolides, aminoglycosides, clindamycin, imipenem, rifampin, vancomycin, cephazolin and other third generation cephalosporin. It is resistant to cefuroxime, extended spectrum antibiotics, like ceftazidime, azotrenam, trimethoprim and sulpha-methoxazole.

CLINICALLY EVIDENT INHALATION ANTHRAX

The recommended initial therapy for adults with clinically evident inhalation anthrax is 400 mg ciprofloxacin given intravenously every 12 hours. The use of dual initial therapy (Ciprofloxacin plus penicillin) may be considered in view of the frequent and rapid development of complicating meningitis and the clinical experience of cerebrospinal fluid penetration.The dose of penicillin G is 4 million unit intravenously every four hour. Doxycycline is another useful drug at the dose of 100 mg intravenously every 12 hour. The most recent (October 26, 2001), CDC recommendations for treatment of inhalational anthrax involve the initial use of ciprofloxacin or doxycycline plus one or two additional antimicrobial agents with in vitro activity against *B. anthracis.*

Because preliminary data have shown the presence of constitutive and inducible betalactamases in recent *B. anthracis* isolates from Florida, New York and Washington DC treatment of systemic anthrax with penicillin G, ampicillin or amoxycillin alone is not recommended.

For mild cases, oral treatment with ciprofloxacin (500mg every 12 hours) is recommended. If the strain is susceptible, oral doxycycline (100 mg every 12 hours) or amoxycillin (500 mg every 8 hours) is a suitable alternative. Treatment should be continued for 60 days in the context of bioterrorism as opposed to 7-10 days for naturally acquired disease.

Severe cutaneous anthrax is treated with the same drugs and dosages as inhalation anthrax.

POST EXPOSURE PROPHYLAXIS

A long period of prophylaxis is recommended for its prolonged latency period in germination of spores acquired through inhalation exposure to *B. anthracis.* Because of the threat of bioterrorist attack and its resistance to multiple antibiotics (Penicillin, doxycycline, chloramphenicaol, macrolides and rifampicin), ciprofloxacin is the drug of choice for initial therapy. Prophylaxis should be continued for 60 days.

An anthrax vaccine, consisting of a noninfectious, sterile, culture filtrate of an attenuated strains of *B. anthracis* is adsorbed to an alumunium hydroxide adjuvant, has been given to members of US armed forces since 1998. The protective component is protective antigen. The vaccine is administered at 0, 2, and 4 weeks and again at 6, 12, and 18 months. Annual booster is necessary to maintain immunity.

Table 2. Recommendations for Post exposure Prophylaxis

Type of Therapy	Adults (Including Pregnant Women and the Immunocompromised)	Children
Initial therapy	Ciprofloxacin, 500 mg orally every 12 hr or Doxycycline, 100 mg orally twice a day	Ciprofloxacin, 10-15mg/kg of body weight orally every 12 hr or Doxycycline, 100 mg orally twice a day in children >8 yr. old and > 45 kg
Optimal therapy if strain has proved susceptible	Amoxycilline, 500 mg orally every 8 hr or Doxycycline, 100 mg orally every 12 hr	Amoxycillin, 500 mg orally every 8 hr in children>20 kg; 40 mg/kg orally, divided into 3 doses (every 8 hr), in children ≤ 20 kg

Vaccine supplies are extremely limited, however, and at present the vaccine is not recommended for use by health care workers or the public. In primates optimal post exposure prophylaxis has been provided by the combination of antimicrobial therapy and immunization. Should the vaccine become widely available, it has been proposed that it's use at 0, 2, and 4 weeks might shorten the antimicrobial therapy to 30 to 40 days.

PROGNOSIS

The mortality rate for cutaneous anthrax is 10 to 20 percent in the absence of treatment but is very low with appropriate antibiotic therapy. In contrast the mortality rate for inhalation anthrax approaches 100 percent and therapy is usually unsuccessful. The mortality rate for gastrointestinal anthrax is approximately 50 percent. Anthrax meningitis is usually fatal.

VACCINATION

The US anthrax vaccine, an inactivated cell free product, was licensed in 1970. The vaccine is licensed to be given in a 6 dose series and has recently been mandated for all US military active and reserve duty personnel. The vaccine is made from the cell free filtrate of a non-encapsulated attenuated strain of *B. anthracis*. The principal antigen responsible for inducing immunity is protective antigen.

A human live attenuated vaccine is produced and was in former Soviet Union. In Western World live attenuated vaccines have been considered unsuitable for use in humans.

Current vaccine supplies are limited and the US production capacity is modest. It will be years before increased production efforts can make available sufficient quantities of vaccine for civilian use. However even if the vaccine were available, population wide vaccination would not be recommended at this time. Given the cost and logistics of a large scale vaccination program and the unlikely occurance of a bioterrorist attack in any given community. Vaccination of some service personnel should be considered if vaccine becomes available.

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Tuberous Sclerosis

A Case Study And Up Date

Md. Ishaque Akhand

INTRODUCTION

A tuberous sclerosis is a rare genetic disorder included in neuro-cutaneous syndrome. It was first described by Von Reclinghausen in 1862 and in 1880, Bourneville used the term Sclerosis tuberose for the potato like lesions in the brain[3]. It is inherited as autosomal dominant but 60% cases are sporadic owing to new mutation[5]. Incidence varies from 1 in 10,000 to 1 in 100,000 of 75% cases having positive family history but rarely detectable when the child is born.

The cardinal features of TS are Skin lesions, Mental retardation from birth and Epilepsy starting usually before 2 yrs of age. Cutaneous symptoms includes-depigmented or hypomelanotic macules, presenting at birth, persisting through out life. Most macules are leaf-shaped, resembling the leaf of the European Mountain Ash tree[3].

Adenoma Sebaceum, a facial angiofibroma, Shagreen patch, connective tissue hamartoma and Cafe-au-lait spots, small fibroma resembling course Googe flesh. There are also some ophthalmic and visceral symptoms-including Phakoma in the retina, Renal tumor and cyst, Rhabdomyoma of heart, Lung cyst, Haemangioma of liver and spleen.

There is no method for prenatal diagnosis[3]. Diagnosis is established by Clinical exam, CT/MRI of brain, EEG etc. Treatment is symptomatic comprising seizure control and management of other complications if any.

CASE STUDY

Nasreen Akhter, an 8 yrs old girl, first issue of her parents, born full term with uneventfully perinatal period to a non-consanguous uneducated lower social parents brought to our paediatric OPD from Rana vola, Uttara, Dhaka, with the complaints of repeated convulsion characterised by brief symmetrical muscular contraction of the face, head & limbs with loss of body tone and tendency to fall causing injury since her 4 yrs of age. She also had irrelivant talks, activity and behavior for the same period. She is self directed home-bound girl showing preference to play with inanimate objects other than playmates.

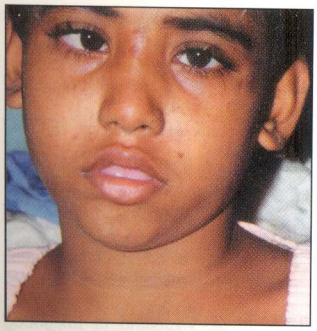

Fig. Girl, aged 8 years, suffering from Tuberous sclerosis, Shows "TUBERS" on her face.

She had two hospital admissions between the ages 1 to 2 yrs for febrile convulsion. She has no hearing or visual problem other than mild bilateral squint but she is unable to talk adequately still now.

All parameters of milestone were delayed since birth. There is no family history of such illness.

Clinically she is hyperactive, showed pranching and parqueting movements with myoclonic type of seizures of early childhood.

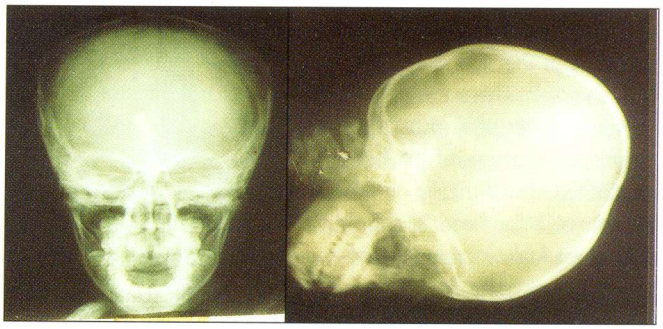

Fig:-2 Plain Radiography of skull shows Calcification (Both AP and lateral film)

Adenoma sebacium was evident on both cheeks, around the nose & forehead exempting the upper lip, sizes varying from pin head to pea & two shagreen patches over lumbo-sacral region. Formal intellectual assessment was not possible & clinical assessment

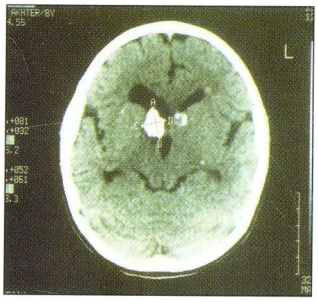

Fig:-3 CT Scan of brain shows periventricular Calcification

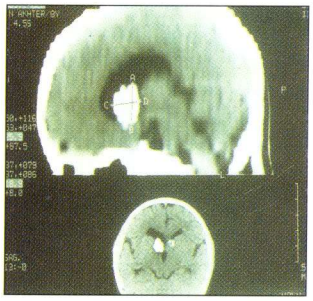

Fig:-4 CT Scan of brain (Reformative scan) Shows obstruction of foramen Monro by calcified tuber there by causing dilatation of frontal horn of Rt. lateral Ventricle

suggested moderate mental retardation.

Fundus occuli examination, Renal function tests, USG of Abdomen, CXR, ECG and Echocardiogram examinations are found normal findings. But cranial EEG reveals brief bursts of spike activity generalized all over the tracing. Skull radiography shows intracerebral calcifications of size (1.5x 1.3) cms. on both views. Non-contrast CT scan of brain shows multiple calcifications of varying sizes in the sub-ependymal locations of the lateral ventricles. Superficial CSF spaces are normal but Rt. lateral ventricle Frontal horn is dilated due to compression over the Foramen Monro by the

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adjacent large calcified mass. Brain-stem and cerebellum shows no abnormality.

Patient was treated by several unregistered and registered doctors with inadequate doses of different anticonvulsants but no improvement was found. When the diagnosis was established, number of attack of convulsion is much decreased and other sign & symptoms are improved.

DISCUSSION

Tuberous sclerosis eponymically is called pringle disease when only dermatological findings are found, Bourneville disease when the NS is only affected and West syndrome when skin lesions are associated with infantile spasm, hypo-arrhythmia and MR[3]. Vogt first emphasized the classic triad of seizure, mental retardation and adenoma sebacium. Adenoma sebacium are not the adenoma of sebaceous gland but are small hamartomas arising from nerve elements of the skin along with hyperplasia of connective tissue & blood vessels. These are not present at birth but become clinically evident in over 90% cases by the age of 4 yrs[3]. At first the facial lesions are the size of pin head or a millet seed & red in colour, distributed symmetrically on the nose & cheeks in butterfly fashion. May involve forehead & chin but rarely affect the upper lip. The lesions gradually increase in size and become yellowish & glistening.

Shagreen Patch, a connective tissue hamartoma usually become evident after 1st decade of life & found in the lumbo sacral region. These are yellowish brown elevated plaques resembling pigmented skin or orange peel. Cafe-au-lait spots, are small fibromas, look like course goose flesh.

Seizures and mental retardation are the indications of diffuse encephalopathy. Infantile myoclonic spasm with or without hypo-arrhythmia, are the characteristics seizures of young infant. Older children has generalized tonic-clonic or partial complex seizures. There is a close relationship between the onset of seizures at young age and mental retardation. Smalley et al, in have autism and mental retardation.

Brain is usually normal in size but several hard nodules occur in the surface of the cortex. The limbs of the Lateral Ventricle is frequently the site of numerous small nodules that project into the ventricular cavity as "Candle Guttering" These nodules consists of clusters of atypical glial cells in the center and giant cells in the periphery. Malignant changes may occur as a progression to form a glioma or spongioblastoma, Glioblastoma & ependymoma[1].

Retinal hamartoma, a phacoma observed in 50% of well studied cases of TS. Visceral abnormality observed includes Hypernephroma, renal cysts, Renal Angiomyolipoma, Rhabdomyosarcoma, Lung cyst, haemangioma of liver & spleen and sclerotic lesion in smalll bones of hands and feet.

Cytogenetically TS is complicated and not due to single gene defect on one chromosome. Chromosome 16 p 13, 3 with a gene product called tuberine appears a major site but 11q-22,23 and possible linkage to chromosome -9 are implicated.

There is no method for prenatal diagnosis but clinical diagnosis is possible at most ages. In infancy three or more macules of 1cm or more size suggests the diagnostic. Involvement may result in dfficulties in the diagnosis of TS. Gomez defined the primary and secondary diagnostic criteria.

Table-1, Diagnostic Criteria for TS[3]

Primary diagnostic criteria	Secondary diagnostic criteria
One of the following criteria: Facial adenoma sebaceum, Periungual or subungual fibroma, Cortical or subependymal tuber, Multiple retinal hamartomas	Two of the following criteria : ◆ Infantile spasm, ◆ Hypomelanotic macules, ◆ Shagreen Patch, ◆ Single retinal hamartoma, ◆ Intraventricular or paraventricular nodular calcification, ◆ Bilateral renal angiomyolipoma, ◆ Cardiac rhabdomyoma.

Important laboratory studies includes : small calcifications within the substance of brain on skull x-Ray, calcified subependymal tubers are better visualized by CT scan and sonogram (in Infant), angiogram are often diagnostic. Renal cyst may be associated with albuminuria or azotemia. IVU are also diagnostic of renal lesions. Chest radiograph may reveal pulmonary lesion or Rhabdomyoma with cardiomegaly. ECG findings are variable but echocardiogram is diagnostic. CSF is normal except when large intracerebral tumor is present. EEG are often abnormal, specially in patient with clinical seizures. Finding of EEG are slow wave activity, arrhythmia, focal or multifocal spike or sharp wave discharge and generalized spike & wave discharge.

There is no specific treatment. Symptomatic management includes, anti convulsants for seizures, shunting for hydrocephalus, behavioral & educational strategies for mental retardation infantile myoclonic spasm often responds to corticosteroid. Focal and generalized seizures are treated with anticonvulsants. Cosmetic surgery for facial adenoma or large shagreen patches. Progressive cystic renal involvement often responds to surgical decompression. Cardiac Rhabdomyoma and CCF are managed medically with cardiotonic, diuretics, obstructive intracavitary tumors require surgical excision of tumor and progressive pulmonary involvement by respiratory therapy.

PROGNOSIS

Mild or solely cutaneous involvement often follows a static course where as those with full blown syndrome have progressive course with increasing seizures and dementia. Brain tumor, status epilepticus, renal insufficiency, cardiac failure or progressive pulmonary impairment can lead to death[3]. Most patient die within a few years after the onset of these complications & severely affected individuals generally die before the age 30[2].

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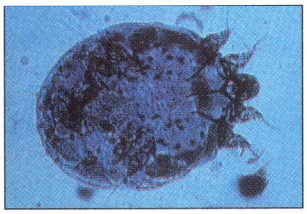
Incidence of Scabies and Scabies-related Acute Glomerulonephritis in Malnourished Children

Mohammad Ali[1], Khaleda Islam[2], H.K.M. Yusuf[3], Salim Sakur[4], Altaf Hossain Khan[5]

SUMMARY

A retrospective study was done on 7,666 patients, who reported at the paediatric Out-patient department of Gogon-Rowshon & Solaiman-Halima (GR&SH) Medical Centre, Lohajang, Munshiganj from May 2000 to April 2001. Among them 643 patients (age-0-15 years) were clinically diagnosed as suffering from scabies. Most of these children (90%) were malnourished (low weight-for-age). Of them, 30 patients (4.6%) developed Acute Glomerulonephritis (AGN). Three hundred and forty scabies patients were treated with Monosulfiram lotion for 3 consecutive days. The recovery rate was 42%. Those who did not recover were again treated for another 3 consecutive days with the same lotion after 1 week interval. This time the cure rate was 99%.

INTRODUCTION



Sarcoptes scabie (variant hominis).

Scabies is a common skin disease all over the world. It is a contagious disease of public nuisance character, caused by a parasitic mite called Sarcoptes scabie. Intimate contact with infected individual or their clothings, malnutrition, low socio economic condition, over crowding, poor hygiene, lack of knowledge are the main predisposing factors. Children below 15 years of age, who constitute 50% of our population, are the worst sufferers. Acute Glomerulonephritis (AGN) may develop in 5% cases from streptococcal infection[1]. It has been observed that better socio-economic condition, with better hygienic living affect less percentage of children[2]. So awareness of people about this is important.

The present paper describes the incidence of scabies and scabies-related AGN in children aged 0-15 years in a rural set-up and the response of the patients to treatment with anti-scabies drug Monosulfiram.

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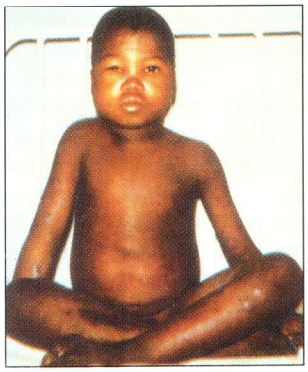

Acute glomerulonephritis. Note facial oedema causing narrowed palpebral fissures, oedema of legs and septic skin lesions.

SUBJECTS AND METHODS

A retrospective study was done on 7,666 patients attending the paediatric out patient department (OPD) of Gogan-Rowshon and Solaiman-Halima (GR&SH) Medical Centre, Lohajang, Munshiganj over the period from May 2000 to April 2001. Among them 643 were suffering from scabies and 30 had Acute Glomeruloneptritis (AGN) due to scabies. Scabies was detected by symptoms like itching, finding burrows and papulovesicle and AGN was diagnosed by clinical examination, history and urine and blood tests[3].

Of the 643 scabies patients, 340 were randomly selected for treatment. The patients were treated with Monosulfiram, Benzyl Benzoate lotion, and Permethrin. Among these, Monosulfiram lotion was found most effective when applied for three consecutive days. Those who did not recover were asked to apply the lotion again for another three consecutive days after an interval of 7 days. In addition, the patients were asked to take scrub hot soap bath and disinfect their clothings.

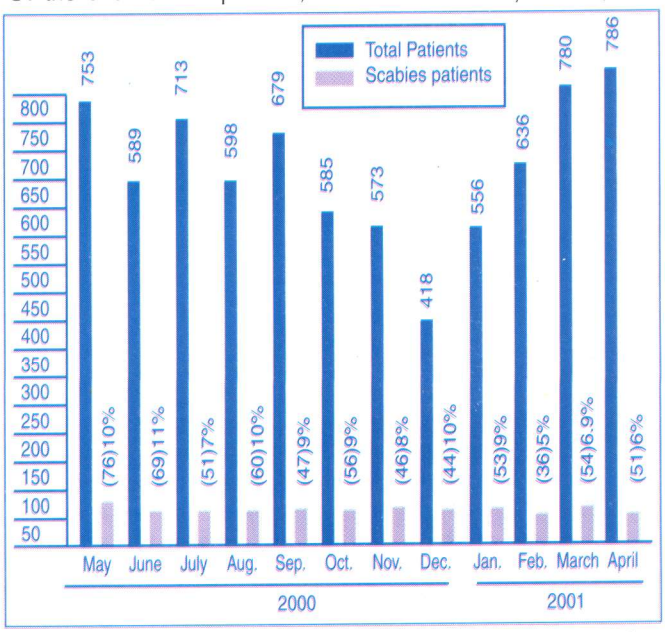

Fig. 1 : Month-wise distribution of total patients and percentage of patients suffering from scabies.

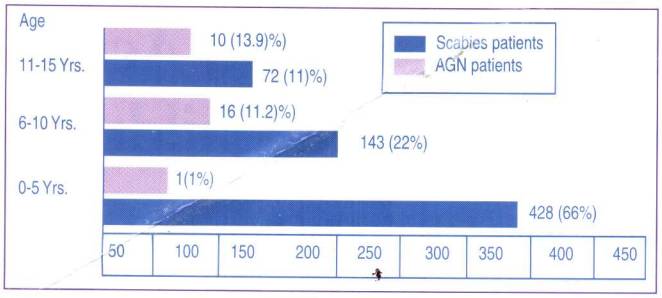

Fig. 2. Age wise distribution of percentage of patients suffering from scabies and percentage of patients from Acute Glomerulonephritis.

RESULTS

Fig. 1 shows the month-wise attendance of total patients in the OPD of the GR & SH Medical Centre, Lohajang, Munshiganj over a period of 12 months from May 2000 to April 2001. It can be seen that the number of patients attending the hospital was lowest during the months of December and January, while the percentage of children reporting with scabies was the lowest during the months of February (5%), March (6.9%) and April (6%) (The average percentage during the whole year was over 10%) (Fig. 1). The winter months are thus the best for health and the early summer months are best for scabies.

Of the 643 patients detected as suffering from scabies, 428 (66%) were aged 0-5 years, 143 (22%) were aged 6-10 years and the remaining 72 (11%) were aged 11-15 years (Fig. 2). This clearly shows that younger children suffer more from scabies than older ones. On the contrary, percentage of children developing AGN was 1% in the age group 0-5 years, 11.2% in the age group 6-10 years and 13.9% in the age group 11-15 years, indicating that incidence of AGN increases as the children grow older.

Table 1: Treatment of patients with Monosulfiram.

Treatment	Total no. Patients	Complete cure	Percentage of success	Treatment failure	Percentage of failure
First three consecutive days	340	145	42.6	195	57.4
Second three consecutive days after one week interval	195	193	99	2	1

Table 1 shows the response of the randomly selected 340 scabies patients to treatment with Monosulfiram. It was found that after local application of the lotion for 3 consecutive days, 145 (42.6%) patients got completely cured. The remaining 195 patients were asked to use the lotion again for another 3 consecutive days after one week interval. After these 3 days, 193 patients (99%) got cured completely (Table 1).

DISCUSSION

The present study shows that scabies is a big health problem for children, particularly those aged 0-5 years. The study was carried out on malnourished children coming from rural areas. The high incidence of scabies among young children indicates the very poor hygienic condition in which they are raised. People should be made aware of this to fight against scabies[4].

One dreadful complication of scabies is Acute Glomerulonephritis (AGN) due to Streptococcal attack[5,6]. More than 4% of the scabies children develop AGN[7]. However, the incidence of AGN was lower in younger children (0-5 years) compared to older ones (6-10 years and 11-15 years). Why this so happens is not clear and this should be investigated further.

One good thing is that scabies is completely curable by drugs like Monosulfiram, best results being obtained with application for 3 consecutive days followed by another 3 days application after a break of one week.

CONCLUSION

The present study shows that scabies is still a major health problem of young children. Poor hygienic living condition and malnutrition are the predisposing factors. People should be aware of these and the children should be given nutritious foods as far as possible. Scabies should be treated immediately after it is detected to avoid complications like Acute Glomerulonephritis which may be dangerous if not treated in time.

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Vaginal Discharge

M. Anwar Hussain

INTRODUCTION

Vaginal discharge is the commonest Gynaecological symptom. The vagina produces a variant amount of discharge normally. It is physiological, small in amount, and it does not cause any irritation or offensive smell. It contains a mixture of secretions from endometrial and endocervical glands, exfoliated vaginal cells, bacterial flora and white blood cells. Excessive vaginal discharge should always be investigated.

Causes of vaginal discharge

Vaginal discharge is not always due to pathological causes. It can be also due to physiological causes.

A) Physiological causes

Important physiological causes are:
1. Immediately proceeding and following menstruation.
2. In the mid cycle
3. After sexual excitement

B) Pathological causes:

Infection: ● Moniliasis ● Trichomoniasis ● Gonorrhoea ● Thread worms infestation in the childhood

C) Foreign body in the vagina : ● Tampons in the adult ● Small Child may introduce foreign body by themselves

D) Erosion : ● Erosion of the cervix

E) Neoplasm : ● Cervical polyp ● Cervical carcinoma ● Vaginal carcinoma

F) Allergy

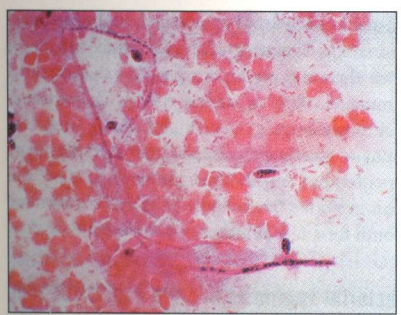
Differential diagnosis of vaginal discharge

Symptoms and signs	Candidiasis	Bacterial vaginosis	Trichomoniasis	Cervicitis
Itching or soreness	++	-	+++	-
Smell	May be 'yeasty'	Offensive, fishy	May be offensive	-
Colour	White	White or yellow	Yellow or green	Clear or coloured
Consistency	Curdy	Thin, homogeneous	Thin, homogeneous	Mucoid
pH	<4.5	4.5-7.0	4.5-7.0	<4.5
Confirmed by	Microscopy	Microscopy	Microscopy and culture	Microscopy, tests for Chlamydia and gonorrhoea

To make the diagnosis, a thorough history and clinical examination followed by relevant investigation is helpful.

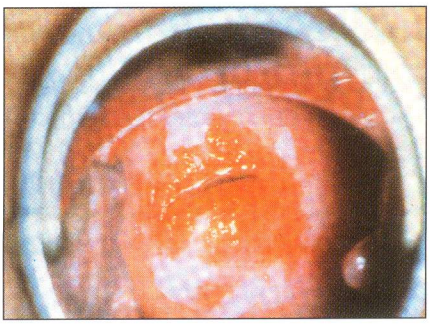
Moniliasis and Trichomoniasis are the two major causes of vaginal discharge with vulvar itching.

Moniliasis is a very common fungal infection of the vagina and vulva. It is caused by Candida albicans. The discharge is typically curdy white. When the white flakes are removed, there appear petechial bleeding. Gram staining will show hypae / pseudohypae. The organism can be cultured in Sabored Agar Medium.



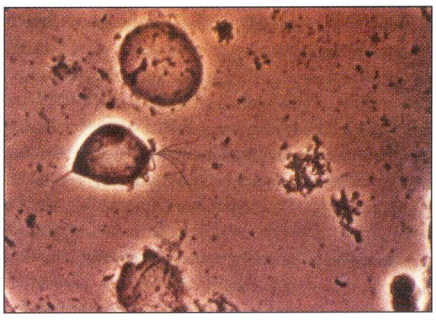
Candidiasis. There are speckled Gram-positive spores and long pseudohyphae visible. There are numerous polymorphs present and the bacterial flora is abnormal, resembling bacterial vaginosis.

Many conditions like oral pill, pregnancy, broad spectrum antibiotic therapy, immunosuppresion, diabetes etc predispose to moniliasis. Infact when there is repeated monilial infection, diabetes should always to be ruled out.



Vaginal candidiasis

Tricomoniasis is caused by the organism Triconads vaginalis. It is a parasite. The discharge is yellowish or yellowish



Trichomoniasis- an unstained 'wet mount' of vaginal fluid from a woman with Trichomonas vaginalis infection. There is a cone-shaped flagellated organism in the centre, with a terminal spike and 4 flagellae visible. In practice the organism is identified under the microscope by movement, with amoeboid motion and its flagellae waving.

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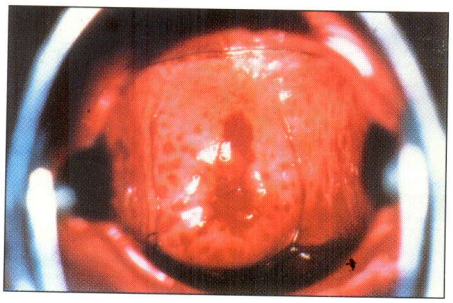

Trichomonal "strawberry cervix"

green and frothy. When examined carefully there appears some punctate bleeding giving the cervix the appearance of strawberry hence it is called strawberry cervix. The orga-nism can also be identified by it's characteristic to and fro movement in hanging-drop preparation. The organism can be identified after gram staining of the discharge. The presence of flagella and undulating membrane is characteristic. The organism may also be cultured. Other conditions causing vaginal discharge can be diagnosed when the women are examined properly.

TREATMENT

The most important thing in the management of these women with vaginal discharge is to distinguish between physiological and pathological cause. There is a superstition that with vaginal discharge they loose energy. So careful counselling is very vital.

Many a occasion we have to exclude the physiological causes and explain that these are not harmful. That is all what they need. Pathological conditions must be needed treatment. A correct diagnosis is very vital. In case of moniliasis, a single dose of 150mg of Fluconazole orally is sufficient to treat this condition. If the husband has uncircumcised penis, he may also be given the same dose of Fluconazole. In resistant cases the duration of therapy may be increased.

Trichomoniasis is a sexually transmitted disease. Both the partners are to be treated simultaneously. Secnidazole 2gm in a single dose with food is sufficient to cure this condition.

Treatment of the other conditions depends upon the cause e.g. cervical polyp to be treated by polypectomy and D&C. Treatment of cervical carcinoma depends upon its stage. Cervical erosion, unless gross is not a cause of vaginal discharge. Before discriminating it, as the cause of vaginal discharge, we shall must exclude all other causes. Only then cautery (electric or chemical) may be done. This is a condition, which is usually over treated.

CONCLUSION

Vaginal discharge is the most common gynaecological symptom. There are some superstitions among our women about vaginal discharge. They should be told that vaginal discharge does not make anybody weak. Every effort should be made to find out the cause of vaginal discharge. In case of physiological discharge, explanation and assurance is the only thing that these patients need, but the treatment of pathological discharge depends upon the cause. We can treat the condition correctly once, we know the cause of discharge correctly.

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MSD News

MSD personnels of Orion Laboratories Ltd. as a part of continued medical education program are arranging seminar in different venues. The members of MSD also spent busy schedule to meet the requirements of valued readers and feedback the correspondences.

Seminar at Barisal

A Seminar was held on Role of Zinc in maternal and child health on 08.11.2001 at medical education unit in Sher-e- Bangla medical College, Barisal. Professor R.K Shaha, Principal of SBMC chaired the seminar and Dr. Amiya Bhushan Deb, Director of SBMCH was present as a chief guest. DR. Md. Shah Alam, Associate Professor and Head of the department of Obs and Gynecology, SBMCH. delivered lecture on "Leaking Membrane-Prematurity and Zinc." Besides this, Dr. A. Hamid Seikh, Assistant Professor, Department of Paedriatics, SBMCH, presented the paper on "Role of Zinc in child health." Dr. ATM Azizur Rahman, Manager, MSD presented the paper on the "Zinc an overview."

Launching of New products

We have recently introduced the following two new products in the market.

1) ***Procap*** (omeprazole)

Procap is a proton pump inhibitor, which is indicated for the treatment of Gastric ulcer, Duodenal ulcer and H. pylori eradication etc. Procap is presented in the form of capsule 20mg and 40mg.

2) ***Cosy*** (Domperidone)

Cosy is a dopamine antagonist who is indicated for the treatment of non-ulcer dyspepsia, esophageal reflux, reflux esophagitis, acute migraine etc. It is presented as Tablet 10mg and Suspension form.

"Drug Resistant Tuberculosis"- A Disgraceful Health Hazards in Bangladesh

Sk. Akbar Hossain

INTRODUCTION

Tuberculosis is an ancient disease of the lungs and is commonly caused by Mycobacterium Tuberculosis. In the era of Hippo crates it was known as Phthisis. About one third of the worlds population was infected by M. tuberculosis world wide in 1997. There were about 9 million new cases of Tuberculosis with three million death. Death from Tuberculosis comprise 25% of all avoidable deaths in developing countries. 95% of Tuberculosis cases and 98% death of tuberculosis occurs in developing countries.

As a consequence the world is facing a much more serious situation in twenty first century than in mid 1950s. Due to Demographic factors, Socio-economic trends, neglected Tuberculosis control program in Bangladesh and in addition the increasing number of HIV, there are many more smear-positive Pulmonary Tuberculosis cases often undiagnosed and/or untreated, poor drug prescription and unskilled case management by village quack and Palli Chikitshak are creating more Tuberculosis patients excreting resistant tubercle bacilli and thus producing more and more Drug-Resistant Tuberculosis patients in Bangladesh which is a real threat to our public health sector.

MDR (Multi Drug Resistant) bacilli are resistant to at least Isoniazid and Rifampicin, the main Anti-Tuberculosis drugs. MDR is the most severe form of bacterial resistance today. That is why MDR Tuberculosis is an important concern for Tuberculosis control in many countries of the world.

HOW IS MDR TUBERCULOSIS PRODUCED

As with other forms of drugs resistance, the phenomenon of MDR Tuberculosis is entirely man-made.

Drug resistant bacilli are the consequence of human error in any of the following

- Prescription of Chemotherapy.
- Management of drug supply.
- Case management.
- Process of drug delivery to the patient.

The most common Medical errors leading to the selection of resistant bacilli are the following

a. The prescription of inadequate Chemotherapy to the multibacillary Pulmonary Tuberculosis cases (e.g, only 2 or 3 drugs during the initial phase of treatment in a new smear-positive patient with bacilli initially resistant to Isoniazid).

b. The addition of one extra drug in the case of failure and repeating the addition of a further drug when the patient relapses after what amounts to mono therapy.

The most common errors observed in the management of drug supply are the following

a. The difficulty experienced by poor patient in obtaining all the drugs that they need (Due to lack of financial resources or social insurance).

b. Frequent and Prolonged shortage of Anti-Tuberculosis drugs (Due to poor management and/or financial constraints of the countries).

c. Use of drugs (or drug combinations) of unproven bioavailability.

The following also have the effect of multiplying the risk of successive mono therapies and selection of resistant bacilli

a. The patients lack of knowledge (Due to the lack of information or due to inadequate explanation before starting treatment).

b. Poor case- management (when the treatment is not directly observed. Specially during the initial phase).

HOW TO PREVENT MDR TUBERCULOSIS

New Cases

The best prevention is to give each new case of Sputum Positive Pulmonary Tuberculosis an effective regimens of short course chemotherapy 6 months or 9 months with four drugs

(Isoniazid, Rifampicin, Pyrazinamide and Ethambutal or Streptomycin) during the first 2 months given under direct observation.

WHO recommended regimen are as effective in patient with bacilli initially resistant to Isoniazid and/or Streptomycin as in patient with susceptible bacilli. The cumulative rate of failure and relapse after 3 years is from 0% - 4% in new cases, 0 - 3% in patients with initially susceptible bacilli and 0-13% in patients with primary resistance.

Old Cases

In this group of Tuberculosis patients previously treated with one or several courses of Chemotherapy and who remain sputum positive (by smear/culture). Three sub-population Can be observed :

- Patient excreting bacilli still susceptible to all Anti-Tuberculosis drug.
- Patient excreting bacilli resistant to at least Isoniazid but still susceptible to Rifampicin.
- Patient excreting bacilli resistant to at least Isoniazid and Rifampicin.

TREATMENT OF MDR TUBERCULOSIS

Designing an appropriate regimen

Designing an appropriate regimen for the individual patient of MDR tuberculosis needs experience and skill. It includes allocating the time and patience to define precisely the following

a. Which regimen(s) the patient had previously received.

b. Whether the patient took all the drugs in each regimen prescribed and for how long.

c. To find out what happened Bacteriologically in terms of sputum positivity at least by direct Smear and Culture and sensitivity test during and after the administration of each regimen.

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Table 1. Ranking of anti-tuberculosis drugs for the treatment of MDR Tuberculosis

Rank	Drugs	Average daily dose	Types of antimyco bacterial activity	Ratio of peak serum level of MIC
1.	Aminogly-cosides a. Streptomycin b. Kanamycin c. Amikacin d. Capreomycin	15mg/kg	Bactericidal against actively multiplying organisms.	 20 - 30 5 - 7.5 10 - 15 5 - 7.5
2.	Thioamides (Ethionamide Prothionamide)	10-20mg/kg	Bactericidal	4 - 8
3.	Pyrazinamide	20-30 mg/kg	Bactericidal at acid PH.	7.5 - 10
4.	Ofloxacin	7.5-15mg/kg	Weakly Bactericidal	2.5 -5
5.	Ethambutal	15-20mg/kg	Bactericidal	2 - 3
6.	Cycloserine	10-20mg/kg	Bactericidal	2 - 4
7.	PAS acid	10-12mg/kg	Bactericidal	100

Table 2. Acceptable regimen for treatment of MDR Tuberculosis before susceptibility test

Initial phase		Continuation phase	
Drugs	Minimum duration in months	Drugs	Duration in months
1. Aminoglycoside 2. Ethionamide 3. Pyrazinamide 4. Ofloxacin	3 3 3 3	1. Ethionamide 2. Ofloxacin	18 18

Table 3. Acceptable regimen if there is resistance to Isoniazid but susceptibility to Rifampicin

Resistance to	Initial phase		Continuation phase	
	Drugs	Minimum duration in months	Drugs	Duration in months
Isoniazid (Streptomycin Thioacetazone)	1. Rifampicin 2. Aminoglycoside 3. Pyrazinamide 4. Ethambutal	2 - 3 2 - 3 2 - 3 2 - 3	1. Rifampicin 2. Ethambutal	6 6
Isoniazid Ethambutal (Streptomycin	1. Rifampicin 2. Aminoglycoside 3. Pyrazinamide 4. Ethionamide	3 3 3 3	1. Rifampicin 2. Ethambutal	6 6

Table 4. Acceptable regimen for the treatment of MDR Tuberculosis

Resistance to	Initial phase		Continuation phase	
	Drugs	Minimum duration in months	Drugs	Duration in months
Isoniazid Rifampicin and Streptomycin	1. Aminoglycoside 2. Ethionamide 3. Pyrazinamide 4. Ofloxacin 5. Ethambutal	3 3 3 3 3	1. Ethionamide 2. Ofloxacin 3. Ethambutal	18 18 18
Isoniazid Rifampicin Streptomycin and Ethambutal	1. Aminoglycoside 2. Ethionamide 3. Pyrazinamide 4. Ofloxacin 5. Cycloserine	3 3 3 3 3	1. Ethionamide 2. Ofloxacin 3. Cycloserine	18 18 18

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Assessment of Coma and Impaired Consciousness- A Critical Review

Anwarul Haider[1], Zillur Rahman[2], J D Sharma[3]

(This article is continued from the previous volume)

Eye Opening Spontaneous eye opening, with sleep/ wake rhythms, is most highly scored on this part of the scale and it indicates that the arousal mechanisms in the brainstem are active. But arousal does not imply awareness, and we believe it is unwise to try to decide whether a patient is attentive on the basis of eye movements. Patients in the vegetative state, who are subsequently shown to be structurally decorticate, have often been believed by relatives, nurses, and even by doctors to be reacting visually to people around them; probably primitive ocular-following reflexes may be executed at subcortical level.

Eye opening in response to speech is a response to any verbal approach, whether spoken or shouted not necessarily the command to open the eyes.

Eye opening in response to pain should be tested by a stimulus in the limbs, because the grimacing associated with supraorbital or jaw-angle pressure may cause eye closure.

PAEDIATRIC COMA SCALE [1-12]

Modified Glasgow coma scale

Eyes Opening

Score	>1 Yr	<1Yr.
4	Spontaneously	Spontaneously
3	To verbal command	To shout
2	To pain	To pain
1	No response	No response

Best Motor Response

Score	>1Yr	<1Yr.
6	Obeys	Spontaneous
5	Localizes pain	Localizes pain
4	Flexion-withdrawal	Flexion-withdrawal
3	Flexion-abnormal (Decorticate rigidity)	Flexion-abnormal (Decerebrate rigidity)
2	Extension (Decerebrate rigidity)	Extension (Decerebrate rigidity)
1	No response	No response

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Best Verbal Response

Score	>5Yr.	2-5 Yr.	0-23 Month
5	Oriented and converses	Appropriate words and phrases	Smiles, coos appropriately
4	Disoriented and converses	Inappropriate words	Cries, Consolable
3	Inappropriate words	Persistent cries or screams	Persistent inappropriate crying or screaming
2	Incomprehensible sounds	Grunts	Grunts, agitated or restless
1	No response	No response	No response

The score of Glasgow coma scale has been modified to be applicable to children, including those who have not learned to speak is the Blantyre coma scale (BCS).

Eyes movements:	directed (e.g. follows mother's face)	1
	not directed	0
Verbal response:	appropriate cry	2
	moan or inappropriate cry	1
	none	0
Best motor response:	localizes painful stimulus	2
	Withdraws limb from pain	1
	Nonspecific or absent response	0
	Total	0-5
	Unrousable coma ≤ 2	

These scales can be used repeatedly to assess improvement deterioration.

a. Rub knuckles on patient's sternum.

b. Firm pressure on thumb nail bed with horizontal pencil.

The child's level of consciousness and the response to stimuli should be carefully documented. A modification of the Glasgow coma scale is a useful tool for the grading of the degree of coma and the severity of the insult in infants and children. It is important to remember that the assessment of the verbal response is much different from that of the adult and the child's developmental level must be kept in mind during the evaluation. A coma score of less than five is associated with a grave prognosis, where as a score of five to eight may indicate a better prognosis in the child than in the adult.

The Glasgow Coma Scale is widely used to assess impairment of consciousness after head injury, both for clinical purposes and in international comparisons of methods of treatment. The scale measures three easily understood neurological reactions: eye opening, verbal responses, and limb movement. For each reaction, a score in points is given, the higher being the better. The three

scores can be aggregated to give a coma score or sum, which indicates the level of responsiveness.

Below the age of 10 years, the verbal responses and to a lesser extent the motor responses, are not easily graded. A frightened child may not be willing to say that he knows where he is, though neurologically unimpaired, a normal infant will not speak or obey commands to move hind limbs. Normally a neonate cannot respond vocally to (by coos, babbles, hums) or locate painful stimuli. Only the eye-opening responses can be measured in the standard manner, even in neonates.

A paediatric modification of the Glasgow coma scale used in the Adelaide Children's Hospital since 1977 (Adelaide coma scale) takes neurological immaturity into account:

Adult scale		Paediatric scale (Adelaide coma scale)	
(a) Eyes open			
spontaneously	4		
to speech	3		
to pain	2	As in adult scale	
none	1		
(b) Best verbal response			
Orientated	5	orientated	5
Confused	4	words	4
Inappropriate words	3	vocal sounds	3
Incomprehensible sounds	2	cries	2
None	1	none	1
(c) Best motor response			
Obeys commands	5		
Localize pain	4		
Flexion to pain	3	As in adult scale	

We have assumed that, during the first 6 months of life, the best verbal response is normally a cry, though of course some infants make vocal responses during this period. The expected normal score at this age is therefore 2. Between 6 and 12 months, the normal infant makes noises; the expected normal score is 3. After 12 months, recognizable words are expected, and the normal score is 4; orientation, defined as awareness of being in hospital, is expected by 5 years. Motor responses are recorded as in the original 5-point adult scale (the 6-point scale, which distinguishes withdrawal from abnormal flexion, has been chiefly used in special units). However, before the age of 6 months, the best normal response is usually flexion (score 3), while in the period 6 months to 2 years the infant will usually locate pain but obey commands (score 4).

Thus, the normal aggregate score will be as follows

Birth to 6 months	:	9
>6 to 12 months	:	11
>1 to 2 years	:	12
>2 to 5 years	:	13
>5 years	:	14

The scales are arbitrary, but accord reasonably well with standard developmental screening tests.

Adelaide and Blantyre (BCS) coma scales compared

Adelaide coma scale	Blantyre coma scale
Motor	
5. Obeys commands	2. Localizes pain
4. Localizes pain	1. Withdraws from pain
3. Flexes to pain	0. No response
2. Extends to pain	
1. No response	
Verbal	
5. Aware of place, able to give name and age	2. Appropriate cry
4. Recognizable and relevant words	1. Inappropriate cry/ moan
3. Incomprehensible, but complex vocalization	0.No cry
2. Cry/ grunt	
1. None	
Eye response	
4. Spontaneous eye opening	1. Directed eye movements
3. Opens eyes to voice	

DISCUSSION[1-27] Apart from its practical use in the management of recently brain-damaged patient, this scales allow the duration of coma to be defined more precisely, in terms of how long different levels of responsiveness have persisted. There is evidence that this is a crucial criterion when it comes to predicting the ultimate outcome of coma, particularly after head injury. It would make it possible also to examine critically claims for good recovery after weeks or months "in coma," by enabling the alleged coma to be more accurately assessed. In such cases as we have scrutinized it has clear, even retrospectively, that there had been evidence of much earlier recovery, on at least one component of the coma scale, then had been recognized. By resolving the problem of defining "prolonged coma" the scale also makes it possible to distinguish between the various states which this term embraces, such as akinetic mutism and the persistent vegetative state.

Some may have reservations about a system which seems to undervalue the niceties of a full neurological examination. It is no part of our case to deny the value of a detailed appraisal of the patient as a whole, and of neurological function in particular, in reaching a diagnosis about the causes of coma, or in determining the probable site of brain damage. However, repeated observations of conscious level are usually made by relatively inexperienced junior doctors or nurses; these staff are not only few in number but they change frequently even during the course of a day. There are therefore good reasons for restricting routine observations to the minimum, and for choosing those which can be reliably recorded and understood by a range of different staff.

Different observers were able to elicit the responses in this scale with a high degree of consistency, and the likelihood of ambiguous reporting appears to be small. This was demonstrated by having several doctors and nurses examine the same group of patients. Disagreements were rare. This was in pronounced contrast to what happened when the observers were asked instead to judge only whether patients were conscious or unconscious; one in five observers then

disagreed with the majority opinion. This 20% disagreement-rate compared with rates of 20-35% which have been reported in various different clinical situations, whilst in one study extensor plantar responses showed only 50% consistency when observations were repeated.

One or other components of this scale may be unstable, and this fact can be recorded. Limbs may be immobilized by splints for fractures, tracheostomy may preclude speech, and eyelid swelling or bilateral third-nerve lesions make eye opening impossible. In the rare "locked-in syndrome," a patient with totally inactive limbs may obey commands to move the eyes and may even be able to signal his needs.

The nurses in our intensive-care unit have willingly adopted this method of formalizing observations which they previously used to record as a descriptive comment. They now plot them on a chart somewhat similar in format, but not content, to one proposed by Bouzarth, and which also provides for conventional recording of temperature, pulse and respiration, of the pupil size in mm and of focal motor signs. This method has already been adopted successfully for making observations on head injuries in a neighbouring general hospital. In such hospitals patients with head injuries form a considerable proportion of acute surgical admissions, and observations there depend on medical and nursing staff who have no special experience of neurology and neurosurgery.

The method for assessing patients with impaired consciousness that described almost a decade age has been widely accepted, and in many centers the eye, verbal, and motor components are summed. Totals up to 8 relate to patients in coma with no eye opening or verbal responses, reflecting changes in motor response; scores from 9 to 15 depend more upon eye opening and verbal responses. Janine jagger and her colleagues doubt if eye and verbal responses add predictive information. They studied the short- term outcome in head- injured patients assessed on admission only. Not surprisingly, they found the motoresponses to be most informative; patients who, on admission, show eye-opening and comprehensible verbal responses ought not to die. Death can be expected only amongst patients already in coma due to severe established brain damage.

Such patients would have no eye opening and no comprehensible verbal responses so that their coma score would depend upon the motor response.

Changes in the eye and verbal responses, and thus higher overall scores, are useful in discriminating between patients with less severe impairment of consciousness. Although these patients would be expected to survive, this may be with differing degrees of disability. The Charlottesville group themselves found that increasing scores in the 9-15 range (reflecting improving eye and verbal performances) are associated with a doubling of the rate of good recovery in survivors of head injury. Furthermore, correlation's have been established across the whole range of the coma score with cerebral metabolic rate for oxygen, evoked potential studies, and biochemical indices of brain damage.

Head-injured patients may change rapidly after admission, and the eye and verbal responses are useful in assessing improvement or deterioration to show whether a patient is in coma and how long he remains comatose. Scores obtained during the first few days after admission reveal much more about prognosis than do admission scores.

The analysis used by the Charlottesville group is not well suited to comparing the relative predictive power of different clinical features and can exaggerate minor differences. Moreover, they included information about pupil responses and about a haematoma, which could not have been known at the time of admission. Yet they have previously demonstrated correlation's between higher coma scores and decreasing frequency of abnormal pupil responses and CT scan abnormalities in moderately injured patients. Because of this, the inclusion of these features may have masked the information provided by the eye and verbal responses. Their analysis should have been restricted to the three aspects of the coma scale. They would then have found that knowledge of the eye and verbal responses in addition to the motor response does convey extra information, whether the three responses are considered separately or summed.

Although we cannot accept the Charlottesville group's reservations about the value of the eye and verbal components there are limitations inherent in the summation of the three responses. This step assumes an equal weighting for the three responses. More importantly, the information conveyed by the coma score is less than that contained in the three responses separately. This is because the same score may be made up in different ways. Indeed, in Glasgow patients under treatment are always described by the three separate responses and never by the total. The total score is merely a convenient method for summarizing data, especially for a series of patients. Therefore, while we do not favour its use in day-to-day clinical practice, we find no reason to doubt that it will continue to be used widely in the analysis and reporting of a series of patients with head injuries or other forms of acute brain damage.

In order to quantify the level of consciousness, a modification of the 'Glasgow' coma scale is developed that was suitable for use in children too young to have learn to speak the Blantyre coma scale (BCS). The scale uses motor and crying responses to pain, and includes ability to watch; from these three criteria a score can be calculated (minimum=0, maximum=5). Score <2 is taken as Unrousable coma.

For research purposes, however, we do not agree with the use of a summation of the Glasgow coma score (GCS) in the definition of cerebral malaria. The GCS was designed to monitor coma and does not provide a complete neurological description of the patient. The summation of the responses is unfounded since their values are determined by their rank order and therefore do not depressant discrete quantities, and in summation of these values, information is lost. These criticisms are especially pertinent to the Adelaide modification if the GCS for children (who bear the brunt of cerebral malaria in Africa) since the responses vary with age. However, the scoring system devised by Molyneux et al is useful

because of its simplicity and independence of age. The world health organization's definition identifies patients in whom the impairment of consciousness cannot be attributed to fever alone, while the score suggested by Leaver et al does not. Unlike Leaver and colleagues, it has found the motor response of the GCS to be the easiest to interpret and have used this in the initial assessment of consciousness in our young patients with malaria. This was also the experience with Thai adults. Thereafter it is reasonable to use coma scores to monitor progress. It is agreed that reports of neurological involvement in malaria should include a stratification of severity, but this should consist of a clinical description of each category and should not be reduced to a single score. Proposals for new definitions and classifications should include full details of the patients on whom these are based, including the parasitological diagnosis and exclusion of other diseases.

Compared with the Glasgow coma scale (GCS), which is objective, reproducible, easily taught, and of proven validity in traumatic and non-traumatic coma. Warrell et al defined unarousable coma as best motor response-localizes or worse; verbal response-incomprehensible sounds or nil; eye opening to pain or nil. This definition, when scored on GCS, gives score of 8 or less. Any upper limit is arbitrary, but it would argue that a patient with malaria and a GCS of 9 - 11 also has cerebral involvement and requires the same management as patients with GCS 8 or less. Such patients would flex or localize in response to painful stimuli; any speech would be confused and disoriented, and the eyes would only open in response to commands or pain.

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Outlines of Urodynamic Studies and Its Clinical Application

M A Salam

(This article is continued from the previous volume).

Bladder pressure measurements during micturition

Opening time is the elapsed time from initial rise in detrusor pressure to onset of flow. This is the initial isovolumetric contraction period of micturition. Time lags should be taken into account. In most urodynamic systems a time lag occurs equal to the time taken for the urine to pass from the point of pressure measurement to the uroflow transducer.

Premicturition pressure is the pressure recorded immediately before the initial isovolumetric contraction.

Opening pressure is the pressure recorded at the onset of measured flow.

Maximum pressure is the maximum value of the measured pressure.

Pressure at maximum flow is the pressure recorded at maximum measured flow rate.

Contraction pressure at maximum flow is the difference between pressure at maximum flow and premicturition pressure.

Postmicturition events (e.g. after contraction) are not well understood and so cannot be defined as yet.

The Stop Test

If this demonstrates the presence of contrast trapped in the posterior urethra, it may indicate bladder neck obstruction. Women, particularly those with stress incontinence are often unable to carry out a stop test.

Isometric Pressure (PISO)

Detrusor pressure measured at the time of the stop test. The significance of the PISO is controversial.

Residual urine

Residual urine is defined as the volume of fluid remaining in the bladder immediately following the completion of micturition.

Normally residual volume should be 0 ml but for practically post void residue more than 100 ml is significant. When residual volume exceeds 300ml the condition may be described as chronic retention of urine.

Post Void Residue (PVR)

- Higher the PVR, weaker the Bladder function or significant BOO
- Normal volume of PVR is 0 ml.
- PVR of 100ml or above is significant.
- PVR over 300 ml indicates chronic retention of urine.

The measurement of residual urine forms an integral part of the study of micturition. However, voiding in unfamiliar surroundings may lead to unrepresentative results.

Important points in the interpretation of residual volume

- When estimating residual urine, the measurement of voided volume and the time interval between voiding and residual urine estimation should be recorded: this is particularly important if the patient is in a diuretic phase.

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- In the condition of vesicoureteric reflux, urine may re-enter the bladder after micturition and may falsely be interpreted as residual time.
- The presence of urine in bladder diverticula following micturition presents special problems of interpretation, since a diverticulum may be regarded either as part of the bladder cavity, or outside the functioning bladder.
- The absence of residual urine is usually an observation of clinical value, but does not exclude intravesical obstruction or bladder disfunction.
- An isolated finding of residual urine requires confirmation.
- PVR less than 100 ml with high IPSS score demands further investigations.

URETHRAL PRESSURE MEASUREMENT

The urethral pressure and the urethral closure pressure are the opposing force to detrusor pressure which represent the ability of the urethra to maintain continence and prevent leakage. In current urodynamic practice, the urethral pressure is measured by a number of different techniques.

Technique

Measurements may be made at one point in the urethra over a period of time, or at several points along the urethra consecutively forming a urethral pressure profile (UPP).

Image

At rest the urethral pressure profile denotes the intraluminal pressure along the length of the urethra. All systems zeroed at atmospheric pressure. For external transducers the reference point is the superior edge of the symphysis pubis. For catheter-mounted transducers the reference point is the transducer itself. Intravesical pressure should be measured to exclude a simultaneous detrusor contraction. The subtraction of intravesical pressure from urethral pressure produces the urethral closure pressure profile.

Intraluminal urethral pressure may be measured :

- At rest (the storage phase), with the bladder at any given volume-resting urethral pressure profile (UPP).
- During coughing or straining-stress urethral pressure profile. The principle of this study is to measure the transmission of pressure from the abdominal cavity to the urethra. In stress incontinence this pressure transmission, which is thought to keep the normal urethra closed during stress, is inadequate. The urethral closure pressure becomes negative on coughing.
- During voiding-voiding urethral pressure profilometry (VUPP). The VUPP is used to determine the pressure and site of urethral obstruction. Pressure is recorded in the urethra during voiding. The technique is similar to that used in the UPP measured during storage.

Techniques of urethral pressure profilometry

Three techniques are described to perform urethral pressure profilometry. The perfusion method, the oldest technique, the balloon catheter profilometry and the most modern catheter mounted transducer technique.

Perfusion method.

A dual lumen catheter with two hole at the tip 5 mm apart is withdrawn down the urethra while the catheter is constantly perfused at a set rate by using a syringe pump. Continuous pressure is monitored through the other lumen of the catheter.

Balloon catheter pressure profilometry

This technique uses a soft balloon mounted on a catheter. The pressure is transmitted by a fluid column to the external pressure transducer.

Catheter mounted Transducer

A miniature pressure transducer is mounted over the catheter when gently pulling out through the urethra it will record the pressure in the urethra instantly. The catheters are highly expansive and too fragile but can provide most accurate data for studying sphincter weakness incontinence(SWI) or stress urinary Incontinence (SUI)

The following parameters recorded in UPP

- Maximum urethral pressure is the maximum pressure of the measured profile.
- Maximum urethral closure pressure is the maximum difference between the urethral pressure and the intravesical pressure.
- Functional profile length is the length of the urethra along which the urethral pressure exceeds intravesical pressure.
- Functional profile length (on stress) is the length over which the urethral pressure exceeds the intravesical pressure on stress.

Comment

Urethral pressure profilometry has, in recent years, enjoyed a disproportionate amount of attention. The results obtained are extremely susceptible to experimental artifacts and the degree of relaxation of the patient. In particular, it must be remembered that this study can be distressingly uncomfortable for the patients-especially males.

The information gained from urethral pressure measurements in the storage phase is of limited value in the assessment of voiding disorders. Total profile length is not generally regarded as a useful parameter.

VUPP is not yet fully developed as a technique and a number of technical, as well as clinical, problems need to be solved before the VUPP is widely used.

ELECTROMYOGRAPHY

Electromyography (EMG) is the study of electrical potentials generated by the depolarization of muscle and in this context, refers to urethral sphincter striated muscle EMG. The functional unit in EMG is the motor unit. This is comprised of a single motor neuron and the muscle fibers which results from activation of a single anterior horn cell. Muscle action potentials may be detected either by needle electrodes, or by surface electrodes.

Technique

Needle electrodes (concentric, bipolar, monopolar, single fibre) are placed directly into the muscle mass and permit visualization of the individual motor unit action potentials.

Image

Surface electrodes (skin, anal plug, catheter) are applied to an epithelial surface as close to the muscle under study as possible. Surface electrodes detect the action potentials from groups of adjacent motor units underlying the recording surface; they can be difficult to secure adequately and provide less reproducible results.

EMG should be interpreted in the light of the patient's symptoms, physical findings and Urological and Urodynamic investigations. The main clinical indication for EMG studies is as an adjunct to video cystometrography to distinguish between striated and smooth muscle in distal urethral obstruction of a neuropathic type. Other EMG studies provide interesting scientific information, which however, rarely alters the clinical management of patients.

Nerve conduction studies

Nerve conduction studies involve stimulation of a peripheral nerve and recording the time for a response to occur in muscle, innervated by the nerve under study.

Reflex latencies

Reflect latencies require stimulation of sensory fields and recordings from the muscle which contracts reflexly in response to the stimulation. Such responses are a test of reflex arcs, which comprise such afferent and efferent limbs and a synaptic region within the central nervous system. The reflex latency expresses the nerve production velocity in both limbs of the arc and the integrity of the central nervous system at the level of the synapse(s). Increased reflex tendency may occur as a result of slowed afferent or efferent nerve production, or due to central nervous system conduction delays.

Sensory testing

Limited information, of a subjective nature, may be obtained during stometry by recording such parameters as the first desire to micturate, urgency or pain. However, sensory function in the lower urinary tract can be assessed by semi-objective tests, which rely upon the measurement of urethral and/or vesical sensory thresholds to a standard applied stimulus such as a known electrical current.

The vesical/urethral sensory threshold is defined as the least current which consistently produces a sensation perceived by the subject during stimulation at the site under investigation; the absolute values will vary in relation to the site of the stimulus, the characteristics of the equipment and the stimulation parameters.

AMBULATORY URODYNAMICS

Urodynamics is the gold standard investigation for the lower urinary tract dysfunction but still a significant number of cases the test is negative. Ambulatory urodynamic monitoring overcomes with some of the limitations with natural bladder filling and the patient is fully ambulant and able to carry out every day activities which may provoke the symptoms.

Techniques of ambulatory urodynamics

The equipment needed for the test is vesical and rectal catheter, a portable data storage device and a personal computer for processing of the data. Image after catheter insertion in bladder and in rectum the battery operated data storage system is connected with the catheters and the patient is encouraged to perform normal activity with the storage device. Next morning the patient return back with the recording device. The data are processed by a computer and the graphs are plotted which may show the type of bladder dysfunction during a particular time.

Comments

Ambulatory urodynamics is highly expansive test with a low sensitivity and specipecity. Despite of high expectation the test has never gained a popularity. For the above reasons this test should be reserved for the most difficult problem.

UPPER URINARY TRACT URODYNAMICS (THE WHITAKER TEST)

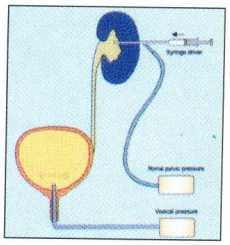

Diagram of the Whitker test

Under normal circumstances, urine accumulates in the renal pelvis at a resting pressure of less than 5 cm H_2O. The pelvic pressure rises to 10 cm H_2O once distended, and urine enters the ureter to be transported as a bolus to the bladder by ureteric peristalsis at pressures between 20-60 cm H_2O. Efficient peristalsis is dependent upon the ureteric walls being able to oppose. Ureteric dilatation, whether obstructive or not, or

disorders of wall mobility prevent the ureteric walls opposing, compromising the Image efficient transport of urine and tubular flow. The normal response of the upper tract to obstruction at, or above, the vesicoureteric junction is an increase in the rate of ureteric and pelvic peristalsis and eventual dilatation. Dilatation causes discoordinated peristalsis and inefficient transport of urine. As flow is reduced down the ureter, pressure rises are first transmitted to the collecting ducts, then along the tubules to the glomeruli. If there is not parallel increase in the glomerular hydrostatic pressure, filtration will eventually stop.

Pressure flow studies involve the perfusion of the kidney with contrast at a known rate, whilst simultaneously measuring the pressure within the renal pelvis and bladder. Significant rises in pressure are indicative of obstruction, whilst free drainage at low pressure excludes obstruction.

Technique

The Whitaker test is performed in the conscious patient at least 24 hours after insertion of a nephrostomy tube. Bladder pressure is measured via a urethral catheter connected to a transducer. Renal pelvic pressure can be measured through a nephrostomy tube, or through a needle placed in the collecting system at antegrade pyelography. Puncture technique needs to be as good as any leak for the collecting system degrades the information that pressure studies will provide. Through one arm of a 'Y' connector, dilute contrast used at an initial rate of 10 ml/min, whilst the other arm of the 'Y' connector is connected to a pressure transducer recording renal pelvic pressure in response to perfusion. Perfusion at 10 ml/min is considered as physiological. The bladder pressure is continuously measured and the subtracted pressure automatically calculated. Such manometric equipment is table in any department performing lower urinary tract dynamics. Simultaneous fluoroscopy defines the anatomy of the bladder tract and spot films can be taken.

Practical points

Using this technique, a pressure difference between the upper and lower urinary tract of less than 15 cm H_2O excludes obstruction. If the renal pelvic pressure exceeds the bladder pressure by more than 12 cm H_2O, obstruction is confirmed.

Pressure differentials between 15 and 22 cm of H_2O lie in the equivocal range. If both the bladder and pelvic pressure rise equally together, vesicoureteric reflux has occurred. Pelvic pressure over 22 cm obstruction is confirmed.

Higher rates of perfusion have been advocated, but are of the debatable clinical usefulness.

In the patient with a urinary diversion, e.g. ileal loop, loin pain is quite frequent because of the high pressures generated by bowel peristalsis refluxing up the reimplanted ureters. The extent of this can easily be assessed by upper tract urodynamics.

Comment

The principal value of upper tract urodynamics lies in allowing an accurate objective assessment as to whether there is obstruction to renal drainage. It is an invasive procedure, since a percutaneous nephrostomy tract is required and therefore its use should be reserved for the case where other investigations, such as excretory urography or isotope renography, have produced equivocal results.

SOME URODYNAMIC DEFINITIONS

Stable detrusor function

During filling the bladder contents increase in volume without a significant corresponding rise in pressure.

Normal detrusor contractility

Normal voiding occurs by a sustained detrusor contraction, which can be initiated and suppressed voluntarily and results in complete bladder emptying over a normal timespan; the magnitude of the recorded detrusor pressure rise is dependent on the outlet resistance.

Overactive detrusor function

Involuntary detrusor contractions during bladder filling, either spontaneous or provoked by rapid filling (provocation cystometry), alterations in posture, exercise or coughing.

The unstable detrusor is one that is shown objectively to contract either spontaneously or on provocation during the filling phase while the patient is attempting to inhibit micturition. The unstable detrusor may be asymptomatic and its presence does not necessarily imply a neurological disorder.

Detrusor hyper-reflexia

Detrusor hyperactivity in the presence of a documented neurological disorder.

Low-compliance

During normal bladder filling little or no significant rise in pressure occurs so-called normal compliance. Although the term low-compliance is applied to a gradual rise in detrusor pressure during bladder filling and is usually taken to imply a poorly distensible bladder, e.g. a shrunken fibrotic bladder complicating interstitial cystitis or after radiotherapy, it must be remembered that both detrusor instability and hyper-reflexia are forms of low compliance and that, at present, there is insufficient data to define normal, high and low compliance.

Underactive (hypocontractile) detrusor function

This is taken to be referring to detrusor activity during micturition. The term underactive applies to all situations where a detrusor contraction is inadequate to produce emptying of the bladder.

Acontractile detrusor

No contractile activity is evident on urodynamic investigation.

Areflexic detrusor

Acontractility resulting from an abnormality of the central nervous system. A specific type occurs with lesions of the conus medullaris or sacral nerve outflow and is known as a decentralized detrusor where the peripheral ganglia in the wall of the bladder are preserved and peripheral nerves are therefore intact. This subgroup is characterised by involuntary intravesical pressure fluctuations of low amplitude, sometimes called autonomous waves.

Destrusor bladder neck dyssynergia.

This refers to a detrusor contraction concurrent with a failure for there to be complete bladder neck opening on micturition. Although rare in the population, it is a common cause of voiding dysfunction in the younger male. In this context it is important to realize that, in recent years, it has been increasingly recognized that an important component of prostatic obstruction results from the contraction of smooth muscle within the pathologically enlarged prostate.

Detrusor sphincter dyssynergia (DSD).

This describes a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated smooth muscle. No similar term has been elaborated for corresponding detrusor/distal urethral smooth muscle dyssynergia. Obstructive overactivity of the striated urethral sphincter muscle may occur in the absence of detrussor contraction, but is not DSD. DSD is usually associated with neurological disorders and, in the absence of a documented neurological deficit, this diagnosis would need to be treated with caution.

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Antioxidants In Diseases and Health

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INTRODUCTION

In recent years, the common people, even of the developing countries like ours, have been becoming health conscious. They frequently enquire their physicians and health workers about the means of living a healthy life. Their main concern is about the vital organs like the heart, brain, lungs, liver and kidneys. They want to know what measures they have to take to run their body machine in an undisturbed way. They are also much interested in prevention of cancers. Thanks to the campaign of pharmaceuticals, newspapers and journals, people have come to know the name of antioxidant vitamins that are supposed to scavenge the free radicals - the first rate criminals that are now considered the final common pathway of cell injury in such varied processes as chemical and radiation injury, oxygen and other gaseous toxicity, cellular aging, microbial killing by phagocytic cells, inflammatory damage, tumor destruction by macrophages and others.[1,2] People want to know what role actually the antioxidant vitamins play in health and in disease prevention. In this article we have tried to compile up-to-date information regarding antioxidants so that practicing physicians, health-care workers and interested students may all be benefited and the enquires of common people may be satisfied.

CHEMISTRY OF FREE RADICALS

A free radical is a molecule that contains an unpaired electron in its outer orbit and that can exist independently. The complete 4-electron reduction of oxygen to H_2O requires 4 steps with the generation of several free radicals (super oxide, hydroperoxy[1] and hydroxy1 radicals) and hydrogen peroxide (H_2O_2).[3,4] H_2O_2, though not a free radical in itself, is considered a reactive oxygen species (ROS) because of its ability to generate highly reactive hydroxy[1] free radicals through interaction with reactive transition metals.[5,6] Each of these oxygen-derived intermediates is considered highly reactive because their unstable electron configuration allows for the attraction of electrons from other organic or inorganic molecules like proteins, lipids and carbohydrates and particularly the key molecules in membranes and nucleic acids. These reactions are auto catalytic in that more free radicals are generated which propagate the chain of damage.

HISTORY OF FREE RADICALS

Although oxygen toxicity was first described in laboratory animals in 1878 and the first experiments regarding a free radical reaction was described in 1894, it was not until late 1940s to early 1950s that retrolental fibroplasias in premature newborns was recognize as being due to oxygen toxicity. However the presence of free radicals in biological systems was not generally accepted until the discovery of super oxide dismutase in 1969.[10]

FREE RADICAL DAMAGE

At least three reactions of the free radicals are particularly relevant to cellular injury

a) ***Lipid per oxidation of membranes***[7] This is the most well described reaction. In vitro, the interactions between free radicals and lipids involve three processes: initiation, propagation and termination. During initiation conjugated are formed through the abstraction of a hydrogen atom from a backbone methylene group of a lipid.[11] This allows the interaction of molecular oxygen with carbon-centered free radicals to form lipid hydro peroxides (also called propagation because of the auto catalytic nature of the reactions generating alkoxy1radicals). Polyunsaturated fatty acids (such as those found in biological membranes) are particularly vulnerable to this process of initiation and propagation because of the multiple unsaturation points found along their backbone. Oxidative damage of membrane results in increased membrane fluidity, compromised integrity and inactivation of membrane-bound receptors and enzymes.[7]

b) ***Oxidative modification of proteins*** This leads to cross-linking of labile amino acids, fragmentation of polypeptide chains and enhanced degradation of critical enzymes.[9,12]

c) ***Lesions in DNA*** such DNA damage has been implicated both in cell killing and in eventual malignant transformation of cells.[13]

There are, however, some inherent mechanisms in healthy body that act to get rid of these free radicals once they are formed. Superoxide, for example, is unstable and spontaneously decays into oxygen and hydrogen

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peroxide. Several enzymes including superoxide dismutase, catalase and glutathione peroxidase act to inactivate different reactive species. There are also the nonenzymatic antioxidants, endogenous or exogenous, that either block the initiation of free radical formation or inactivate the free radicals.[13] We are principally interested in this latter group of substances in the current article.

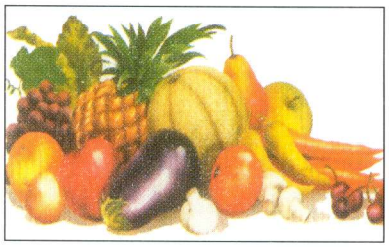
THE ANTIOXIDANTS

The antioxidants constitute a diverse group of compounds with different properties. They operate by inhibiting oxidant formation, intercepting oxidants once they have formed, and repairing oxidant-induced injury. The word antioxidant has become a household term, and every day we are bombarded with claims of antioxidant protection against a host of diseases. Diseases as diverse as atherosclerosis, cancer, gastric ulcers, memory loss, rheumatoid arthritis, endometriosis, pregnancy complications, hypertension and stroke have been suggested to be induced by oxidative stress and antioxidants are claimed to be beneficial in the prevention and treatment of these disorders. Let us have a critical look into the accumulated evidence for and against such claims. First we shall discuss the antioxidants in general.

The most commonly used antioxidants are: vitamins A, C, E, carotenoids (including alphacarotene, beta-carotene, lycopene, lutein, and zeaxanthin, among others); alpha-lipoic acid; coenzyme Q·10; oligomeric proantho-cyanidins (OPCs); and trace minerals (manganese, selenium, and zinc). Among these the most important are vitamins A, C, and E and the carotenoids such as beta-carotene and lycopene.

1. **Vitamin-A** Beta carotene, the precursor to vitamin-A found in vegetables, has antioxidant properties. Natural vitamin-A sources include: dairy (milk, yoghurt, cheese), eggs, fish liver oil, and butter.
2. **Natural caroteinoid** Beta-carotene, lycopene, lutein and zeaxanthin

   Beta-carotene (vitamin-A precursor) is a highly efficient antioxidant. Natural beta-carotene sources include yellow-orange and green vegetables and fruits, such as apricots, broccoli, cantaloupe, carrots, mangos, papaya, spinach, sweet potatoes, and turnip greens.

   Lycopene, which gives tomatoes their red color, has been found in a number of studies to be a 10-times-more-potent antioxidant than beta-carotene. Lycopene sources include tomatoes and tomato products, such as tomato sauce, pizza containing tomatoes, watermelon, red grapefruit, and guava.

   Lutein and zeaxanthin sources include: dark-green, leafy vegetables, such as spinach, collards, kale, mustard greens, and turnip greens.
3. **VITAMIN C** Vitamin-C is a great health-protecting nutrient, as well as an outstanding antioxidant for defusing free radicals. Natural sources include: acerola cherry (juice); strawberries; cranberry juice; guava; fresh orange and grapefruit juices; papaya; and red peppers.
4. **VITAMIN-E** Vitamin-E is a major factor in protecting cell membranes. However, it is next to impossible to get an adequate daily dose of vitamin-E through the diet. The richest sources have relatively low amounts of the vitamin; also, the best foods are high-calorie, high-fat oils and nuts. Examples are wheat-germ oil, soybean oil, almonds, and hazelnuts.

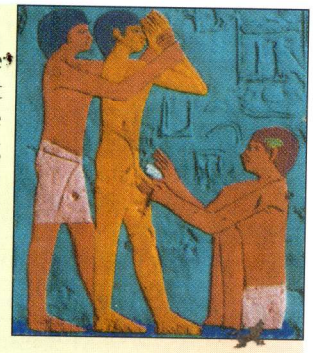
   
5. **ALPHA-LIPOIC ACID** Alpha-lipoic acid vigorously scavenges free radicals everywhere in the body. While vitamin-C, being water-soluble, can battle free radicals only in a water medium, and vitamin-E, being fat-souble, can fight them only in a fat medium, alpha lipoic acid can snuff them out in both a water and fat medium. It also enhances the effect of other antioxidants. Natural sources include: spinach, broccoli, and organ meats.
6. **OPC's (oligomeric proanthocyanidins)** OPC's are derived from grape skins, grape seeds, French maritime pine bark, and green and black teas. OPC's are 20 times more powerful than vitamin-C and 50 times more so than vitamin-E. Moreover, OPC's team up with vitamins-C and E to make them even more potent antioxidants.
7. **Flavonoids** Quercetin (from onions, apple skin, berries, black grape, tea, and broccoli) and rutin (from buckwheat) have antioxidative activity that aid normal prostate function and help in protecting against breast cancer. Quercetin and myrecetin, which are extracted from Ginkgo biloba leaves, ate said to protect brain tissue from oxidative damage.
8. **CURCUMINOIDS** These compounds are found most conspicuously in the roots of turmeric (Curcuma longa), that has antioxidant compounds which operate in two ways. First, its compounds help prevent the buildup of excess free radicals; second, already formed (excess) free radicals are neutralized by the action of free-radical scavenging.
9. **TRACE MINERALS** Among these are selenium, copper, zinc, and manganese, some of which serve as cofactors for enzymes with antioxidant activity (eg, glutathione peroxidase and superoxide dismutase). However, little information is available on the preventive effects of these nutrients in human populations.
10. **COENZYMES** Coenzyme Q10 is known as a potent antioxidant. Another coenzyme, NADH (nicotinamide adenine dinucleotide), helps to form reduced glutathione (which, in turn, can rejuvenate vitamins C and E). Natural sources of NADH are: meat, poultry, and fish; vegetables contain very low levels of this coenzyme. In fact, vegetarians can develop an NADH deficiency over time, which can be combated be supplementation.

Rest of this article will be published in next issue of "The ORION"

Medi News

News from Internet/Journal

CIRCUMCISION AND HIV

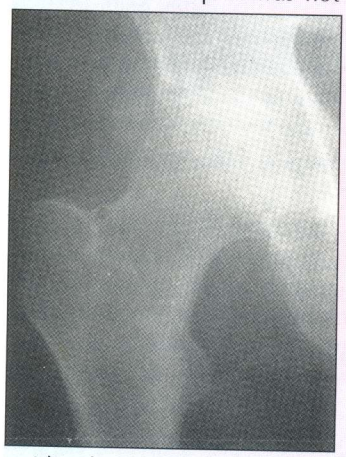


Male circumcision is a practice dating back at least to ancient Egypt. The accompanying image is adapted from a relief carving on the wall of the Tomb of the Physician, Saqqara, Egypt. Now circumcision is Being proposed as an HIV prevention strategy, because, as reviewed by Robert Bailey and colleagues, recent studies have shown a significant association between lack of male circumcision and risk of HIV infection.

BENZODIAZEPINES AND HIP FRACTURES

A case-control study was carried out to determine whether benzodiazepines are associated with an increased risk of hip fracture in elderly people. The study involved 245 cases of hip fracture not related to traffic accidents or cancer in patients over 65 years of age who were admitted to the emergency department of a university hospital, matched to 817 controls.

It was found that the use of benzodiazepines as determined from questionnaires, medical records or plasma samples at admission to hospital was not associated with an increased risk of hip fracture (odds ratio 0.9,, 95% confidence interval 0.5-1.5). However, it was found that hip fracture was associated with use of two or more benzodiazepines, as determined from medical recorders and questionnaires (but not from plasma samples). Of individual drugs, only lorazepam was associated with increased risk of hip fracture (1.8, 1.1-3.1).



The study concluded that, with the exception of lorazepam, the presence of benzodiazepines in plasma was not associated with an increased risk of hip fracture, although the method used to ascertain exposure could influence the results of case-control studies.

Pierfitte C, Macoullard G, Thicoipe M et al (2001) Benzodiazepines and hip fractures in elderly people: case-control study. Br Med J 322: 704-8.

WHAT SHOULD I DO IN ASTHMA AS AN EMERGENCY?

Emergencies are not common; with early recognition and treatment, it is usually possible to bring asthma under control. However, in a severe episode or sudden attack the child would be:

- distressed
- gasping for breath
- pale and quiet
- finding it hard to speak
- out of it or unresponsive
- unrelieved by medication

Use the acronym ASTHMA to help you remember how to deal with an asthma attack:

Assess

Is the attack mild, moderate, or severe? If the child has severe asthma or is frightened, call an ambulance immediately.

Sit

Sit the child down comfortably, leaning forward with arms supported. Stay with him, Reassure calmly.

Treat

Get the child to take six puffs or doses of a reliever inhaler. Use a spacer for aerosol inhalers if available (one puff at a time in a spacer, while the child takes six breaths).

Help

If your child doses not improve after five minutes, call for medical assistance and an ambulance. Continue to use the reliever inhaler-six puffs every five minutes-until help arrives. In this situation, you will not overdose the child by giving him the reliever every five minutes.

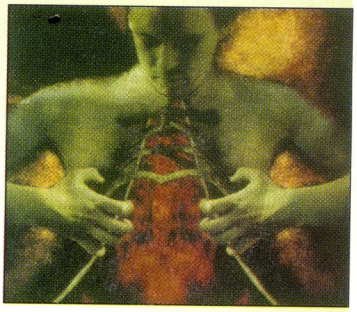
Monitor

Continue monitoring even if the child improves after five minutes. If necessary, repeat the doses of reliever inhaler.

All O.K.

When the child is free of wheezing, cough, or breathlessness, allow him to resume normal activities. If symptoms recur, take the child to the doctor.

STOP THE BURN TONIGHT



Night heartburn robs sleep. Here,s even more troubling news. Stomach acids can do more damage to the esophagus when you're lying down, increasing cancer risk. Take these tips for better sleep and health.

6 p.m. : Eat light. Try to eat your main meal and high-fat treats early in the day. Fat can relax muscles in the esophagus, causing reflux.

8 p.m. : Last call. No munchies or meals after 8.00. Your stomach needs a full 3 hours to empty out before bedtime.

10 p.m. : Time your pills right. Over-the-counter antacids and prescription drugs that decrease the flow of stomach acids work better if you take them right before bed.

11 p.m. : Sleep on your left side. The esophagus enters the stomach on your right side. Sleeping on your left prevents any remaining food in your stomach from pressing on the opening to the esophagus, which could cause reflux.

Sefin

Cephradine

Still A Leader in the Effective Management of Infectious Diseases