GLAXO ORATION

HYPERBARIC OXYGEN THERAPY IN DERMATOLOGY

Group Captain R K Dutta

Mr Chairman, Prof. VR Metha, distinguished delegates from India and abroad, ladies and gentlemen, I offer my sincere thanks to the Chairman for his generosity and kindness and the floral tributes given to me. I am extremely grateful to Dr R.G. Valia, Chairman of the Scientific Committee and all members of his team for inviting me to deliver this prestigious 'Glaxo Oration' to this August gathering. I regard this indeed as a great honour and consider it as one of the most glorious events in my life that a member of Indian Association of Dermatologists, Venereologists and Leprologists could aspire for. Glaxo Laboratories India Ltd., is one of the pioneer institutions in India. The company is well known and is famous for its dedicated services to the suffering humanity.

For today's oration, I have selected a new and challenging subject "Hyperbaric Oxygen (HBO) Therapy in Dermatology", the field where I have some personal contributions.

Introduction

Hyperbaric oxygen therapy, though new to many of us, has been known for centuries. Its developmental history is not only interesting but also rewarding. It begins in the distant past with man's initial exposure to hyperbaric condition through diving in quest of food, treasures, escape and pleasures. Diving has been practised for thousands of years by pearl divers of the Indian and Pacific Oceans.

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The first recorded attempt to use hyperbaric chamber in medicine was made by the British doctor, Henshaw in 1662. He used elevated pressure for acute, and low pressure for chronic diseases. His chamber was known as domicilium. His remark about the domicilium was far reaching and interesting, "In time of good health, the domicilium is proposed as a good expedient to help digestion, to promote insensible respiration, to facilitate breathing and of excellent use for prevention of most affections of lungs."

An historical account of hyperbaric oxygen would not be complete without mention of Priestle's great discovery of oxygen in 1775, who projected the possible therapeutic use of oxygen in medicine and remarked, "From the greater strength of vivacity of the flame of a candle in this pure air, it may be conjectured that it might be peculiarly salutary to the lungs in certain morbid cases." After breathing pure oxygen he remarked "The feeling of it to my lungs was not sensibly different from that of common air, but I fancied that my breast felt peculiarly light and easy for some time afterwards; who can tell but that in time, that this pure air may become a fashionable article of luxury. Hitherto only two mice and myself have had the privilege of breathing it".

Soon after invention of the air pump by Triger in 1841, experiments with compressed air in medicine started in specially equipped chambers. The use of hyperbaric treatment was restricted to France upto 1860. Many chambers were built in France, Holland and England. It was worth noting the luxurious surroundings, often associated with the treatment

centres. It invited wealthy men and women from all parts of the world for hyperbaric treatment. All types of diseases were being treated, even singers and obese ladies came in for intermittent treatment to improve their voices and to beautify their figures. The interest in HBO was so much that William of Brompton Hospital remarked in BMJ in 1885, "The use of air under different degrees of atmospheric pressure in the treatment of disease is one of the most important advances in modern medicine. We are astonished that in England, this method of treatment has been so little used".

1887 to 1950 is considered a lean period in the history of hyperbaric oxygen. A lot of the over-enthusiasm had faded away. A HBO chamber to many scientists was nothing more than an interesting laboratory tool that provided new possibilities in a hunt for scientific papers. However, the value of HBO therapy noted in the previous years, has been more than psychological effects only.

After the lean period, a new interest was kindled. The fame of hyperbaric therapy rapidly spread over Europe in 1950s. Many consultants started keeping a small chamber in their consulting rooms. The first chamber was built in USA in 1960. In India, HBO therapy was first started at the Institute of Aviation Medicine, Bangalore in 1967 and a second centre soon followed in Bombay. Today there are five such centres in India.

The hyperbaric oxygen was introduced in clinical practice in a big way in mid fifties following the pioneer work of Boerema in Holland and Illingworth and Davidson in England. Since then, it has never looked back. A lot of innovations and works were undertaken by the scientists and doctors to develop the modern HBO chamber for medical use. The modern day chambers are of two types; multiplace and monoplace. For research purpose, small chambers are available to study the effect of HBO on microbes and on experimental animals. Pressurised operating theatres have also been set up in many centres.

Physiological basis of HBO therapy

HBO was originally introduced with the general idea that a large amount of oxygen could be made available deep into tissues, specially the vital organs for their survival, in the event of or prior to circulatory arrest. It could also be of immense value in many pathological conditions where normal amount of oxygen is not available while breathing air at 1 ATA.

Table I. Alveolar gas tension (mm Hg) at 37°C.

	Alveolar gas coposition on			
	Breathing air	Breathing 100% oxygen		
		1 ATA	2 ATA	3 ATA
PN_2	570	0	0	0
PH_2O	47	47	47	47
PCO_2	40	40	40	40
PO_2	103	673	1435	2193

On switching to 100% oxygen breathing, a rapid rise of alveolar partial pressure of O_2 results. N_2 is washed out in 7 minutes. Alveolar gas compositions at different atmospheric pressures are shown in table I. Oxygen can be transported in the blood, chemically as oxygenated haemoglobin, or physically in solution in plasma and in intra-cellular fluid in the RBCs. Because of peculiarity of the oxygen dissociation curve, the increase in oxygen tension can hardly take place as oxyhaemoglobin. However, the amount of dissolved O_2 increases with the increase of pulmonary O_2 tension. O_2 tension in the arterial blood is the primary factor which governs the volume of O_2 to be carried in both forms. Average arterial tension of 90 mm Hg may rise to 550 mm Hg while breathing 100% O_2; at 3 ATA, the average value may be upto 1700 mm Hg. Actual O_2 tension in any particular organ depends on the tissue activity and blood flow. Greater discrepancies

may occur in pathological states from one region to another.

In recent years, a number of diseases have been treated with HBO with very good results. However, due to lack of control studies, proper therapeutic evalution has not been possible. To gain a worthy place, HBO therapy must be : (i) Uniquely beneficial and superior to other modes of therapy, (ii) fully practical in its use, and (iii) applicable to a reasonable number of patients.

The diseases hitherto treated with HBO are classified into different categories according to their effectiveness either as a primary mode of therapy or as an adjunct to routinely prescribed treatment.

Category 1 : Disorders for which HBO is the primary mode of treatment or at times adjunctive; but without doubt, beneficial include, (i) Carbon monoxide poisoning, (ii) Decompression sickness, (iii) Gangrene, (iv) Air embolism, and (v) Tetanus.

Category 2 : Conditions for which results on animal studies and clinical experience are encouraging, but for which available controlled studies are few include : (i) Burns, (ii) Head and spinal cord injury, (iii) Cardiac surgery, (iv) Ischaemia, (v) Osteomyelitis, and (vi) Radionecrosis.

Category 3 : Diseases for which animal studies and clinical experience have shown promising results, but definite evidence that HBO therapy is superior to other forms of therapy is yet to be proved. These include : (i) Cerebrovascular accidents, (ii) Delayed healing of fractures, (iii) Non-healing ulcers, and (iv) Trophic ulcers.

Category 4 : Disorders for which HBO has been used empirically and found beneficial. In this group a number of diseases are included such as arthritis, malignancy, traumatic shock, vascular injuries, psoriasis, lichen planus, erythema nodosum, scleroderma, Schamberg's disease, toxic melanoderma, fungal disease, etc.

Indication for HBO therapy and its scope in dermatological practice are steadily increasing. It is being used in non-healing ulcers, fungal diseases, collagen disorders, bacterial infections, cutaneous vasculitis and other infective disorders like leprosy, tuberculosis etc.

HBO and non-healing ulcers

Beneficial effect of HBO in quickening the healing process has been proved in treating refractory cases of varicose ulcers, osteomyelitis and septic conditions. The earliest observation was that of divers who noticed that their cuts healed more rapidly while at work. Because of facility available at Bangalore, I had an opportunity to treat 3 cases of non-healing ulcers and two cases of trophic ulcers due to leprous neuritis with HBO, not responding to conventional therapy. The first patient had multiple abscesses with discharging sinuses and ulcerations of 3 months duration. No specific diagnosis could be made. *Streptococcus β-haemolyticus* were grown in culture, sensitive to gentamicin, ampicillin and septran. The patient showed no improvement with antibiotics and local therapy (Fig. 1). The second patient had multiple

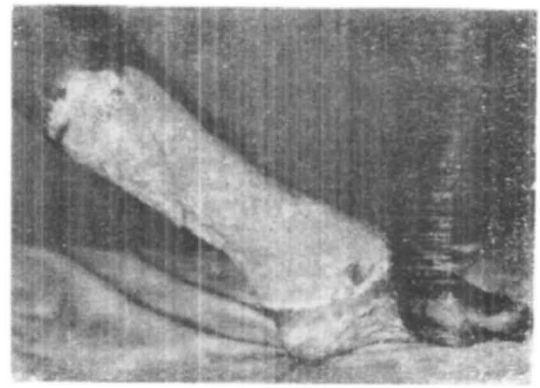

Fig. 1. Extensive ulceration with sinuses.

abscesses and punched out ulcers with a copious sero-purulent discharge. Tender abscesses

continued to appear in crops over the extremities. An abscess in the left eye produced scleral perforation through which uveal tissue could be seen. No specific diagnosis could be made. Culture had grown *Staphylococcus pyogenes* sensitive to gentamicin, chloromycetin and septran. Antibiotics and routine therapy had no effect (Fig. 2). The third patient had deve-

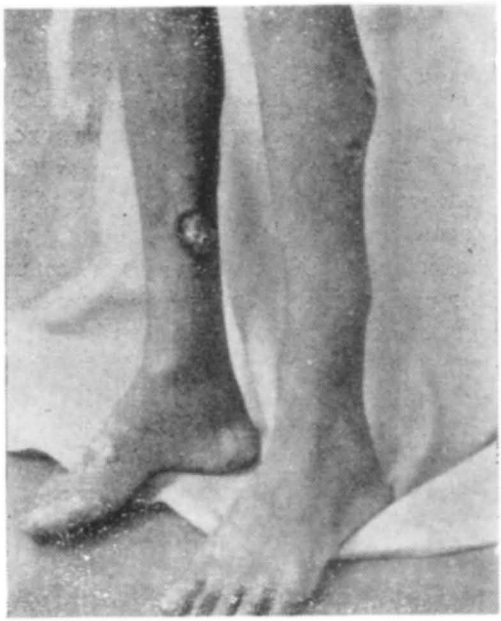

Fig. 2. Punched out ulcers and multiple abscesses.

loped extensive ulcerations over both extremities. Ulcers over the shoulders resulted after gentamicin injections. Antibiotics and local therapy had no appreciable effect (Fig. 3). Two cases of plantar trophic ulcers due to neuritic leprosy not showing adequate response on routine therapy were also included for HBO therapy. All these patients were subjected to hyperbaric oxygen therapy for 60 minutes daily at 2.5 ATA as an adjunct to routine therapy. After 1 week of therapy, the ulcers started healing and the cultures became sterile. Ulcers completely healed in 3 weeks time. The beneficial effect was attributable to enhanced fibroblastic activitiy, neo-vascularisation, formation of granulation tissue and epithelisation. Bactericidal and

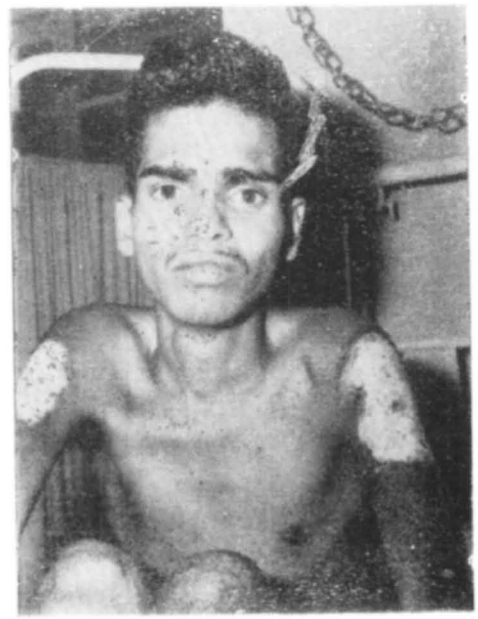

Fig. 3. Extensive ulcerations over the shoulders after gentamicin injections.

bacteriostatic effects of HBO on aerobic organisms were of additional help in quickening the healing process.

HBO and fungal diseases

Mc Allister et al (1964) and Bornside (1978) have recently treated fungal diseases with HBO, as an adjunct to normal therapy. They observed enhancement of fungicidal activity by 80 to 100% due to deprivation of CO_2 and high O_2 tension at tissue and cellular level. When HBO was given alone as a primary mode of therapy, although HBO was found toxic to fungi, it failed to produce a cure.

Chronic ulcerative nature of the disease and encouraging reports of HBO therapy on fungal diseases, prompted me to try HBO on sporotrichosis. Two cases of sporotrichosis were subjected to HBO therapy as an adjunct to iodide therapy. Treatment with iodide though satisfactory in general, takes a long time for lesions to heal and often, the treatment

had to be stopped due to toxicity and intolerance to iodides. Both the cases of sporotrichosis that were subjected to HBO therapy were of the cutaneous lymphatic type.

The patients were subjected to HBO exposures 60 minutes daily at 2.5 ATA along with iodide therapy. After 1 week, the lesions started showing improvement and the culture became negative on repeated examinations. Ulcers healed in 2 weeks time. Potassium iodide was continued for another one week and there was no relapse during one year of observation. This could be regarded as a preliminary report and controlled studies on a number of cases would prove its worthiness as a therapeutic measure.

Hyperbaric oxygen and candidiasis

Bornside in 1978 studied the effect of HBO on 21 different strains of yeasts isolated from the humans, 8 strains belonging to *Candida albicans*. He exposed these strains at 1 and 3 ATA. After 24 hours exposure to 100% O_2 at 1 and 3 ATA, he found that HBO at 3 ATA was particulary sensitive. Indices of kill were found to be 81% in 17 out of 21 strains. Hyperoxia at 1 ATA was not lethal. I sincerely believe that there is an immense scope for further studies of HBO on generalised candidiasis.

Effects of HBO on anaerobic and aerobic organisms

On the basis of their gaseous requirements, bacteria are divided into aerobes, obligate anaerobes and facultative anaerobes. The distinction lies chiefly in the response of the organisms to molecular oxygen and CO_2. Anaerobes are distinguished by their need for exclusion of molecular oxygen because it is reduced by the flavoproteins to hydrogen peroxide which is toxic to these organisms. Hyperbaric oxygen is considered lethal or detrimental to the growth of anaerobic organisms. This fact had been fully utilised in treating cases of clostridial infections specially those of gas gangrene and tetanus.

While noting the inhibitory effect of HBO on anaerobic organisms, the question arose as to what would be the effect of hyperbaric oxygen on aerobic organisms. As early as 1878, Bent had described the toxic effects of HBO on bacteria and yeasts. First clinical application was made in the same year when a Spanish physician successfully used HBO at 2 ATA in healing a young man with pneumonia. Later, Mc Allister and his colleagues (1964) demonstrated the antimicrobial effect of HBO in acutely infected animals. They studied the effect of HBO on a number of common human pathogens such as *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa.* The results were compared with controls incubated in the air at 1 ATA. HBO was found toxic to all these organisms. It produced inhibition of growth rather than destruction of the organism.

Bornside (1967) and Brown et al (1978) conducted intensive studies on antibiotic sensitivity and observed enhanced activity of polymyxin B against *Pseudomonas aeruginosa* under HBO. There was however, a set-back, since many feared emergence of unknown or altered pathogenic bacteria, but the fact remains that therapeutic response has always been good on experimental animals and patients suffering from aerobic infections, when HBO was used as an adjunct to conventional therapy. The possible mechanism was thought to be due to the formation of super-oxide ion and oxygen toxicity to bacteria.

A study was undertaken along with a pathologist colleague of mine at Bangalore, to find out the effect of HBO on common aerobic organisms such as *Staphylococcus aureus* and *Streptococcus haemolyticus.* There was a marked inhibition of growth of the organisms under

hyperbaric conditions, with a marked reduction of the viable count. Besides bacteriostatic and bactericidal effects, antibiotic sensitivity of staphylococci and streptococci to penicillin was greatly enhanced under HBO.

HBO therapy in systemic scleroderma

Systemic scleroderma is a chronic, progressive connective tissue disorder with multi-system involvement. At present there is no satisfactory therapy for generalised scleroderma. Corticosteroids do not appear to effect the process. The role of immuno-suppressive and low molecular weight dextran is the subject of much discussion.

Presently, Dowling et al (1967) and Barr et al (1972) treated a few cases of generalised scleroderma in the advanced stage of the disease with HBO. They observed regression of the skin contraction, improved mobility of the joints and healing of persistent ulcerations. Marked improvement of the Raynaud's phenomenon was observed in all the cases. We treated, 2 cases of systemic scleroderma and one case of polymyositis with HBO therapy with an idea to give them some relief of their distressing symptoms. The first patient, a 48-year-old lady had stiffness of skin and joints, Raynaud's phenomenon, and recurrent ulcerations of 5 years duration. Multiple, tender and hard swellings were present over the extensor aspects of forearms, thighs and buttocks with multiple sinuses discharging chalky material. Movements of peripheral joints were restricted and painful. There was no clinical or radiological evidence of systemic involvement. Chalky material was found to be calcium deposits (Fig. 4).The second patient was a 16-year-old girl, an established case of systemic scleroderma with Raynaud's phenomenon, thickening of skin, dyspnoea and loose motions off and on, of 3 years duration. There was hyperpigmentation of face, sclerodactyly with multiple ulcers on the finger tips (Fig. 5). X-ray showed re-

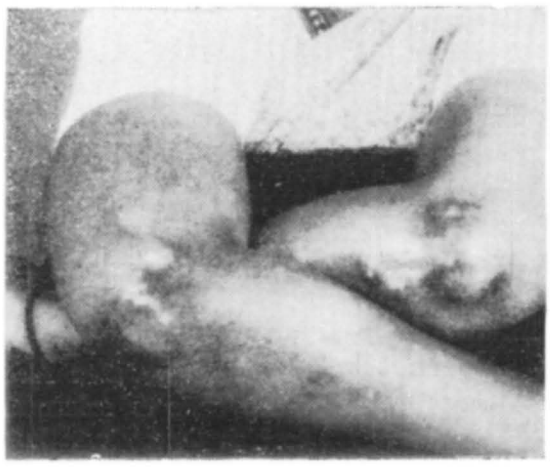

Fig. 4. Multiple ulcerations with calcium deposits.

Fig.5. Stiffness of the skin and multiple ulcers over the finger tips.

absorption of terminal phallanges and a barium swallow showed atonic dilatation of the oesophagus. The third patient, a 30-year-old lady, was a case of polymyositis and had stiffness

and erythema on the face and fingers. There was difficulty in swallowing liquid and solid foods and weakness of the pelvic and shoulder blade muscles which were tender. Finger tips were erythematous with dilated nail fold capillaries. She had short courses of corticosteroids earlier with temporary benefit.

All the three patients were subjected to HBO at 2.5 ATA for 60 minutes daily for 20 exposures. There was a marked physical improvement of the skin and joint stiffness. There was no Raynaud's phenomenon and the ulcerations seen in the first patient healed up. There was a marked improvement in the case of polymyositis. Weakness and tenderness of the muscles disappeared in 3 weeks time. The cases are being followed up for any recurrences.

Hyperbaric oxygen and cutaneous vasculitis

The beneficial effect of HBO has been reported in the treatment of vascular occlusive disorders, TAO in particular. During the last 17 years, IAM, Bangalore has treated a vast number of cases of TAO and other chronic peripheral vascular disorders transferred from all over India. In one study, out of 58 cases, 55 showed marked improvement in different parameters. The angiographic pattern of vessels showed new collateral formations and opening up of blocked vessels. Majority of the cases came for treatment very late when other methods of therapy had failed. If the cases could be treated early when the pathological changes would be of lesser magnitude, chances of cure and result with HBO therapy may be expected to be more rewarding.

This has opened up a tremendous scope for HBO therapy in managing cases of cutaneous vasculitis. It has received endorsement from panelists at the annual meeting of the American Academy of Dermatologists. Lazarus found HBO a very dynamic form of therapy. The best outcome was observed by Freedberg in cases with livido reticularis and cases affecting smaller vessels. Similar result was also observed by Dowing et al.

In recent years, a number of bewildering array of diseases have been treated with HBO with beneficial results. Babayants and Matveeva (1978) treated lichen planus, Schamberg's disease, psoriasis and toxic melanoderma with HBO. Significant improvement was reported in 69 out of 74 cases. In all these cases, this treatment was given as a component of a composite therapy.

Side effects

HBO is not free from toxic effects. Each case has to be properly evaluated before HBO therapy is instituted. Lung pathology favouring air trapping is an absolute contra-indication to this mode of treatment. Chronic respiratory diseases with CO_2 retention become worse with HBO which not only removes the hypoxic stimulus but also favours its retention by interfering with its removal by Hb. HBO is to be avoided in infants where it is likely to cause blindness due to retrolenticular degeneration. HBO can increase blood pressure by 25-40 mm Hg in a hypertensive patient. Steroid is also known to increase O_2 toxicity and is to be avoided during HBO exposures. Patients with epilepsy are not suitable subjects for HBO therapy which may precipitate convulsions in them.

The most common side effect of HBO therapy is barotitis causing earache and even rupture of the drum. A slow increase in pressure, instructions in pressure equalisation of the middle ear by valsalva and in worst cases, myrengotomy usually solve the problem.

Oxygen toxicity may involve CNS and produce severe convulsions especially when pulmonary O_2 tension is higher than ATA. Diazepam helps in these cases to reduce the sensitivity of CNS to high O_2 tension. Lung tissues may be damaged if exposures are given for a long time. Short exposures and alternative

treatment guard against lung damage. Molecular oxygen is a potent enzyme inhibitor and can oxidise some of the important non-protein constituents of the cells into inactive forms, thereby producing a state of hyperoxic hyperoxia leading to cellular death and cell disruption. Lastly, fire risk in oxygen rich environment should not be forgotten.

Current trend

A large number of hyperbaric centres are now functioning all over the world. These are in many cases organised on a regional basis. Some HBO centres have developed in association with a group of specialist units such as ICU, thoracic surgery, neuro-surgery, orthopedic, malignant diseases and renal units. Many therapeutic chambers have been established in some Air Force and Navel units and off-shore oil industry to meet the hazards of decompression associated with flying and diving activities.

The present day interest in HBO has resulted in an almost re-evaluation of all the previous findings. The ultimate fate of the large number of HBO chambers in different centres remains to be seen. In large centres, its place will probably be permanent. It will be worthwhile to study whether HBO has any role in the ageing process and in rejuvination.

I thank you for your kind and patient hearing.