

**THE THERAPEUTIC USE
OF
INTRAVENOUS
HYDROGEN PEROXIDE**

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**A Review
Experimental Evidence of Physiological Effect
and Clinical Experience.**

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A primary clinical objective in the treatment of Chronic Degenerative disease is to improve micro-circulation to relieve chronic tissue hypoxia. The relief of tissue hypoxia has been the subject of many investigative studies.

Early investigators infused oxygen intravenously with limited success. Mariani¹ in 1904 treated a dying tubercular patient with intravenous oxygen. The patient's pulse and respiration improved but the treatment was not repeated and he expired the following day. In 1916, Tummiccliffe and Stebbing² found they could inject 600-1200 ml of oxygen per hour intravenously without causing gaseous embolism. This relieved the cyanosis of their critically ill patients. The clinical benefits of the oxygen infusion appeared greater than explained by the relief of cyanosis alone. Later, in 1940, Singh and Shah³ treated 6 patients with severe pulmonary disease using 10 to 20ml of oxygen injected per minute. The patients all improved, indicated by increased blood pressure and pulse. These investigators also noted the clinical improvements were beyond what should be expected from the small amounts of oxygen produced.

Oliver⁴ first reported the use of hydrogen peroxide (H₂O₂) in 1920 in patients with Influenzal Pneumonia. An epidemic in Busrah in June and July of 1919 had a calculated death rate over 80%. Oliver treated 25 patients with intravenous infusions of H₂O₂ and 13 fully recovered reducing the mortality to 48%. ***He was impressed with the rapid clinical response and postulated the effects were probably due to the oxidation of toxins more than the relief of hypoxia.*** Hydrogen peroxide used in surgical procedures has caused air embolisms but he reasoned if the oxygen was released slowly, embolism should not occur. Venous oxygen embolism has been reported following the irrigation of anal fistulae⁵, surgical wounds⁶ and closed body cavities⁷. Ulcerative colitis⁸ has been produced in patients using H₂O₂ in enema solutions to break up fecal impactions. Hydrogen peroxide solutions are used as a topical antiseptic agent but Shemp⁹ found infusions of H₂O₂ have no bacterial static or bactericidal effect in-vivo in the treatment of experimentally induced Escherichia coli sepsis. It has been shown, however, to destroy marine malaria parasites¹⁰ and the bactericidal properties of H₂O₂ produced by neutrophils is well documented by others^{11,12,13}.

Several lay persons have reported the oral ingestion of H₂O₂ has relieved symptoms associated with their chronic degenerative diseases. The combination of fatty acids, likely to be in the stomach, in the presence of iron and ascorbate, may reduce H₂O₂ to hydroxyl and superoxide free radicals^{14,15}. The action of free radicals, especially hydroxyl, may have a deleterious effect upon the gastric and duodenal mucosa. A. Ito¹⁶ showed an increase of glandular stomach erosion, duodenal hyperplasia, adenoma and carcinoma in mice fed H₂O₂ orally in concentrations as small as 0.8% for ten weeks. More recent studies¹⁷ of gastric carcinogenesis in rats, however, found 1% oral H₂O₂ for 32 weeks did not increase tumor formation after N-methyl-N'-nitro-N-nitrosoguanidine initiation.

All body tissues and fluids contain an abundance of catalase¹⁸. Hydrogen peroxide in the presence of catalase is reduced to oxygen and water. There are numerous reports using intra-arterial and intra-venous infusions of H₂O₂ in concentrations from 0.008% to 0.6%^{19,20,22,23,24}. ***These studies would represent several hundred patient infusions, safely administered, with no reported serious side effects.*** Regional perfusion of H₂O₂ to increase the radiosensitivity of cancerous tissue is well documented. Whether the increase in radiosensitivity is due to oxygen, free radicals or H₂O₂ is still being debated^{21,51}. The rate and concentration of infusion is limited by bubble formation which may cause gas embolism or pulmonary edema. Intravenous H₂O₂ has been found useful as contrast media in echocardiography^{25,26,27,28} because of the bubble effect and its use has been reported to be safe and effective.

There is a species difference of catalase content between man and animals. The results of many animal experiments may not be applicable to man. Dogs and chickens have low catalase levels and poor tolerance to H₂O₂. Pulmonary edema and methemoglobin results from low catalase levels²⁹. Catalase is abundant in both plasma and red cells of man and is significantly elevated in synovial tissues in rheumatoid arthritis¹⁴. Early studies¹⁸ of H₂O₂ infusions predicted the half life was less than 1/10th of a second. More recent studies by Macnauthton^{21,31} calculated the half life ranges from .75 to 2 seconds and are dependent upon the rate of mixing. Hydrogen peroxide initially reacts with catalase in the plasma and white cells. Later, it penetrates the cell membrane of erythrocytes where it reacts with intracellular catalase and additional oxygen is released. The rate of penetration depends upon membrane protein peroxidation as evidenced by the formation of spectrin-hemoglobin complex and is not related to lipid peroxidation³³. MacNaughton demonstrated, when H₂O₂ was infused into the blood stream, there was laminar flow and very poor mixing even in tortuous vessels. Turbulence did not appreciably effect the mixing rate. Others³⁰ have estimated the peroxide-reaction life as long as 12 seconds.

Intravenous infusion of H₂O₂ did not significantly affect blood pressure or pulse²⁴, hematocrit or differential blood studies²⁹, sodium, potassium, calcium, chlorides, magnesium or pH and urine studies were negative²³. Intra-arterial infusions caused no change in formed blood elements except when injected into the carotid arteries. Carotid perfusion causes a significant increase in all formed blood elements particularly in the platelet count³⁴. Hydrogen peroxide has a protective effect on ischemic myocardium³⁹ and has been used successfully to convert ventricular fibrillation⁴⁰. Cholesterol and triglycerides become elevated after intra-arterial injection of H₂O₂. ***Repeated intra-arterial infusion has been found to remove arthromatous plaques and increase elasticity of the blood vessel walls***^{24,32}.

When H₂O₂ is injected into the blood stream it exists for a fraction of a second to several seconds in the free state. The delay of H₂O₂ reacting with catalase in the plasma, then later in the erythrocytes, indicates complex intermediate metabolism. ***The products of h₂o₂ metabolism may be responsible for the observed clinical improvements not attributed to the increased oxygen. The benefit of oxygen saturation of tissue fluid from the oxygen produced¹⁸ by H₂O₂ may be of secondary importance. Hydrogen peroxide is a powerful oxidizer and will oxidize toxic and nontoxic substances alike. The clinical effects we have observed from intravenous infusions of H₂O₂ may best be described as "Oxidative Detoxification".*** The oxidative benefit may include the oxidation of lipid material in the vessel wall to reverse atherosclerosis³². Further evidence of the benefits of oxidative detoxification is found in a discussion by Weiss¹¹. Activators of neutrophils include aggregated immunoglobulin, activated complement components, immune complexes or bacterial peptides. These activators can stimulate the neutrophils to discharge lysosomal enzymes and generate oxygen metabolites (H₂O₂) which will cause their oxidation and destruction. Our observations of intravenous H₂O₂ rapidly relieving allergic reactions, influenzal symptoms, chronic systemic candidiasis, acute viral reactions are considered the results of the oxidation of antigenic substances. A H₂O₂-myeloperoxidase-Cl system generates hypochlorous acid (HOCl) also a powerful oxidant^{41,42}. Tumor cells, bacteria, several biological targets, amine, amides or sulfhydryl groups can all be destroyed by HOCl^{43,44,45}. The tumoricidal effect of H₂O₂ in vivo has also been demonstrated by Nathan⁴⁶.

Oxygen saturation of biological tissue fluids by intra-arterial or intra-venous injection of H₂O₂ is independent of pulmonary function, alveolar diffusion, oxygen transport systems or hemoglobin content. Intravenous H₂O₂ has been used experimentally to supply up to 20% of an animal's oxygen requirement²⁰. Oxygen tension in tissues generated by H₂O₂ may reach 3 to 12 atmospheres, the same as tensions accomplished with Hyperbaric Oxygen³⁵. Several attempts to measure tissue pO₂ comparing

hyperbaric oxygen, intra-arterial and intra-venous infusions of H₂O₂^{35,36,47} are in poor agreement. The studies of Germon et al.^{36,47} measured tissue pO₂ using a micro-oxygen electrode. They found tissue pO₂ produced by intra-venous H₂O₂ is not significantly different than breathing 100% oxygen by mask. They recorded three different patterns of tissue oxygen saturation with H₂O₂. The first pattern shows a direct linear relationship between arterial and tissue pO₂. The second pattern showed a substantial delay of 20-30 minutes before increased pO₂ could be measured. The third pattern was flat with no response up to 35 minutes. No explanation was given for these different patterns.

Ackerman et al.³⁵ made a comparison between hyperbaric oxygen and intravascular H₂O₂ tissue pO₂ also using the micro-oxygen electrode for measurement. They found the micro-oxygen electrode was not precise and consistent measurements were subject to technical error. Their studies showed tissue pO₂ paralleled the increase in hyperbaric oxygen pressure. They also found tissue pO₂ paralleled the intra-arterial infusion of H₂O₂ but increased tensions were not recorded until 40 to 45 minutes after the beginning of the injection. This may explain why the third pattern described by Germon showed no change in 30 minutes. Ackerman also found an ordinary intravenous injection of H₂O₂ did not raise the tissue pO₂ a measureable amount. They speculated any increased venous pO₂ would be lost by diffusion as the blood passes through the pulmonary capillaries. The validity of this assumption is explored further in this paper.

The rates of wound healing, stasis and vascular ulcers¹⁹, peripheral occlusive disease³⁷, myocardial ischemia²⁴ and cerebral vascular disease³⁸ have all improved when treated with repeated intra-arterial infusions of H₂O₂.

Finney et al.³⁹ were able to show, when DMSO was added to the H₂O₂ infusion mixture, there was an increased tissue penetration of oxygen in dense fibrous myocardium. Additional benefits may be realized, utilizing DMSO with H₂O₂, since DMSO is a scavenger of hydroxyl radicals⁴⁸. DMSO protects biological systems from the damaging effect of free radicals by its capacity to be oxidized⁴⁹. In this study of multiple enzyme systems, no significant irreversible loss of enzymatic activity was caused by DMSO.

Preparation of Hydrogen Peroxide Solutions

Reagent grade 30% H₂O₂ is used to prepare our infusion solutions. Hydrogen peroxide, USP food or cosmetic grades are avoided because they contain tin and phosphate compounds to stabilize the H₂O₂ molecule. Concentrated H₂O₂ solutions are powerful oxidizers and should be handled with caution. The 30% H₂O₂ is diluted with equal amounts of sterile distilled water to make a 15% "stock" solution. The stock solution is passed through a Millipore 0.22um medium flow filter for sterilization and removal of particulate matter. The stock solution is stored in 100ml sterile containers and kept refrigerated ready for future use. Our infusion solutions are prepared using sterile 5% dextrose in water. The addition of 1 ml of the 15% H₂O₂ stock solution to each 100ml of carrier solution will produce a 0.15% concentration used for intravenous infusions.

Studies on bubble formation with H₂O₂ in blood by Johnson³⁰ found bubbles formed in concentrations of 0.87 millimolar, but not at 0.69 millimolar. A 0.15% solution of H₂O₂ infused at the rate of 4 ml per minute, assuming a blood flow rate of 100ml per minute, will give a 0.006 volumes percent blood concentration. This produces 2.9 ml of oxygen per 100ml of blood.. Concentrations above 0.01 volume

percent cause bubble formation and are detrimental to capillary circulation. If we double our mixture concentration to 0.3% it will effectively increase the oxygen produced from 2.9ml to 7.0ml per 100ml of blood. This would produce a concentration of 0.012 volumes percent, exceeding the 0.01 volumes percent found to cause bubble formation and capillary damage. The lungs are remarkable filters of microbubbles⁴⁹, however, their capacity can be exceeded and continuous infusions of 0.01 volumes percent may lead to irreversible pulmonary damage and arterial embolism.

During our early studies of intravenous H₂O₂, an infusion of 0.3% may have produced hemoptysis in one subject, although he had previously received five infusions of 0.3% without side effect. Several investigators^{19,32,36} have used concentrations up to 0.48% intra-arterially without side effects, but we do not recommend these concentrations.

Caution must be exercised that nothing is added to the H₂O₂ solution because of its tremendous oxidizing power. Even ascorbic acid is rapidly oxidized to the monodihydroascorbate radical¹⁴, an unstable compound which degrades into numerous other chemical fragments. A principle physiological action of ascorbic acid in tissue, however, is through the formation of H₂O₂⁵⁸. ***Vitamins, minerals, peptides, enzymes, amino acids, heparin, EDTA, or other injectible materials should never be mixed with the H₂O₂ solution.***

Preliminary Studies with Hydrogen Peroxide

Most of the previous studies with H₂O₂ have employed the intra-arterial route of administration. Little attention has been given to effects of H₂O₂ when given intra-venously. It has been assumed H₂O₂ given intravenously would have no metabolic effect since oxygen produced would diffuse into the aveolar spaces from the pulmonary capillary beds. If the life of the peroxide-oxygen reaction is more than a few seconds, the H₂O₂ may be systematically distributed before it is completely reduced to oxygen and water. The incorporation of H₂O₂ into the metabolic pathways appears to be far more complex than appreciated in previous studies. No postulation was forwarded to explain why there was a 40 minute delay from the beginning of the intra-arterial infusion to the rise of pO₂ in muscle tissues. If H₂O₂ is degraded into oxygen and water immediately, according to statements in previous studies, and oxygen administered by mask or in a hyperbaric chamber causes an immediate increase in tissue pO₂, then what accounts for the findings that a 40 to 45 minute delay occurs before an increased tissue pO₂ is measured after the intra-arterial infusion of hydrogen peroxide?

If oxygen, released from intravenous H₂O₂, diffuses from the pulmonary capillary bed into the alveolar space, alveolar pO₂ will rapidly increase and pulmonary capillary blood pO₂ would decrease. Diffusion into the alveoli will occur more rapidly than the alveolar loss of oxygen through respiratory exchange. Inspired oxygen added to the oxygen diffused into the alveoli from the pulmonary capillary at the arterial end would increase the alveolar pO₂ greater than the blood pO₂ at the venous end of the capillary. The increased pO₂ in the alveolus would cause the oxygen to rapidly diffuse back into the pulmonary capillary at the venous side and back into the systemic circulation. One of the following experiments is designed to test this postulate.

Methods

Two experiments were conducted. The first was to measure the metabolic effect of H₂O₂ and the second to measure the vascular effect.

A computerized constant oxygen measuring instrument manufactured by Waters Instruments, Inc. was used to measure the oxygen content of inspired air. *The rate of oxygen consumed by the body per unit of time and lean mass is a measurement of metabolic rate.* The instrument, a MRM-1, is extremely sensitive to changes in oxygen concentration, easily calibrated and its results are highly reproducible. Test subjects were considered to be within the norm for their age with no known pulmonary pathology. They had fasted for a period of at least 6 hours before each experiment. During the experiment they remained at absolute rest in a comfortable reclining chair. A plastic mask, which completely covers the face, is worn during the experiment. The mask collects all expired air and directs it over a sensor to measure oxygen content. The instrument is balanced against the ambient pO₂ in inspired air. The difference is expressed as milliliters of oxygen consumed per minute per kilogram of lean weight. Each subject was given intravenous injections of 100 and 250 ml of 0.15% of H₂O₂ alone and again with 500 mgm of DMSO added per each 1 ml of the 15% stock solution of H₂O₂ used. The solutions were administered in the antecubital area using a standard infusion setup with a 25 gauge needle at a rate of 50 to 60 drops per minute.

Frequently our test subjects had a flushed appearance after an infusion and expressed a feeling of warmth. This observation lead to speculation H₂O₂ may have a different effect on the arterioles and capillary beds from the vasospasm reported to occur in the larger arteries and veins.

Photoplethysmographic recordings were made at 5 minute intervals, measuring pulse volumes in the right index finger before, during and following the infusion of 250 ml of 0.15% H₂O₂. Continuous temperature measurements were also made using a sensitive thermistor placed in the right axilla throughout the same infusion. The measurements were made using a Model 2100 Vascular Analyzer.

Results

An increase in metabolic rate begins to be recorded in less than 2 minutes after the beginning of the infusion. There is a linear peak increase in metabolic rate until a maximum or 'peak' rate is reached. The rate plateaus and remains constant throughout the duration of the infusion. The averaged results of these experiments are illustrated in Figure 1.

The maximum rates recorded were the same at all concentrations and represented an increase in metabolic rate of approximately twice the baseline level (100% increase). The metabolic rate increase appears to be an 'all-or-none' phenomenon and not related to H₂O₂ concentrations. The metabolic rate returns to the baseline level within 20 to 30 minutes after the infusion is discontinued. The increase is independent of the carrier, either 5% dextrose in water or normal saline. A similar pattern was found in all subjects rested and was reproducible in each subject with repeated infusions.

METABOLIC RATE RESPONSE TO INTRAVENOUS INFUSIONS OF H₂O₂ AND DMSO

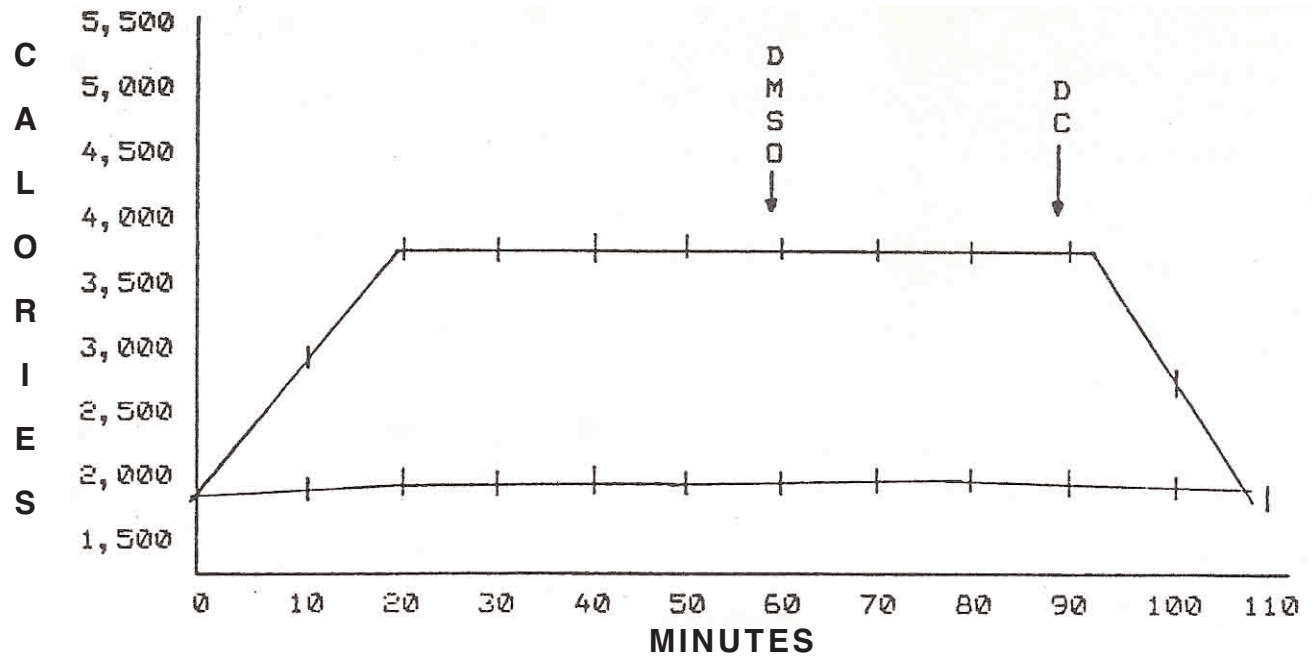


FIGURE 1 (above):
 (Upper Line) The averaged metabolic rate response of 5 test subjects receiving infusions of 250 ml of 0.15% H₂O₂ in 5% Dextrose in water. (Lower Line) The average metabolic response of 3 test subjects receiving only 5% Dextrose in water. One and one-half (1 1/2g) grams of DMSO was added approximately half way through the infusions.

EFFECT OF H₂O₂ CONCENTRATION ON METABOLIC RATE INCREASE

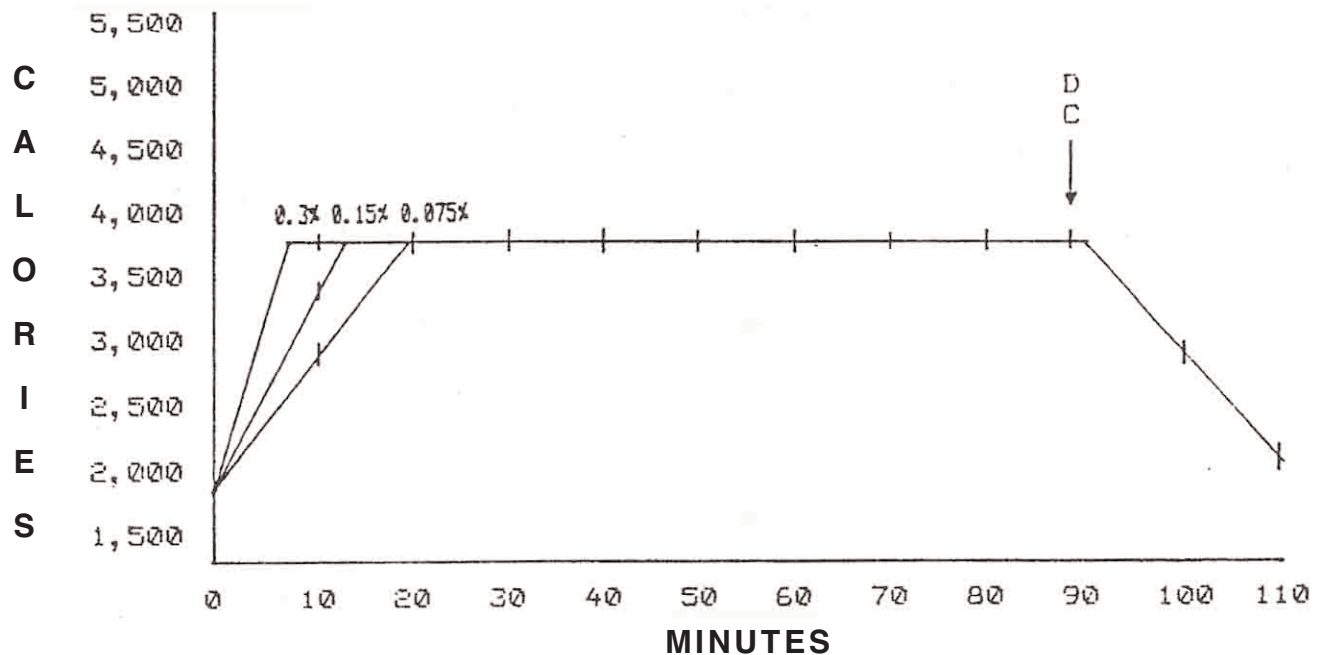


FIGURE 2 (above):
 Rate increase of metabolic rate in response to three different concentrations of intravenous infusions of Hydrogen Peroxide. Maximum metabolic rate plateaus at all concentrations and remains constant for the duration of the infusion. The rate of increase in the metabolic rate is related to the H₂O₂ concentration. The peak rate is reached in approximately 20 minutes with a concentration of 0.075%, 13 minutes with a 0.15% and 7 minutes with a 0.3% H₂O₂.

EFFECT OF H₂O₂ ON TEMPERATURE AND DIGIT BLOOD FLOW

Temperature

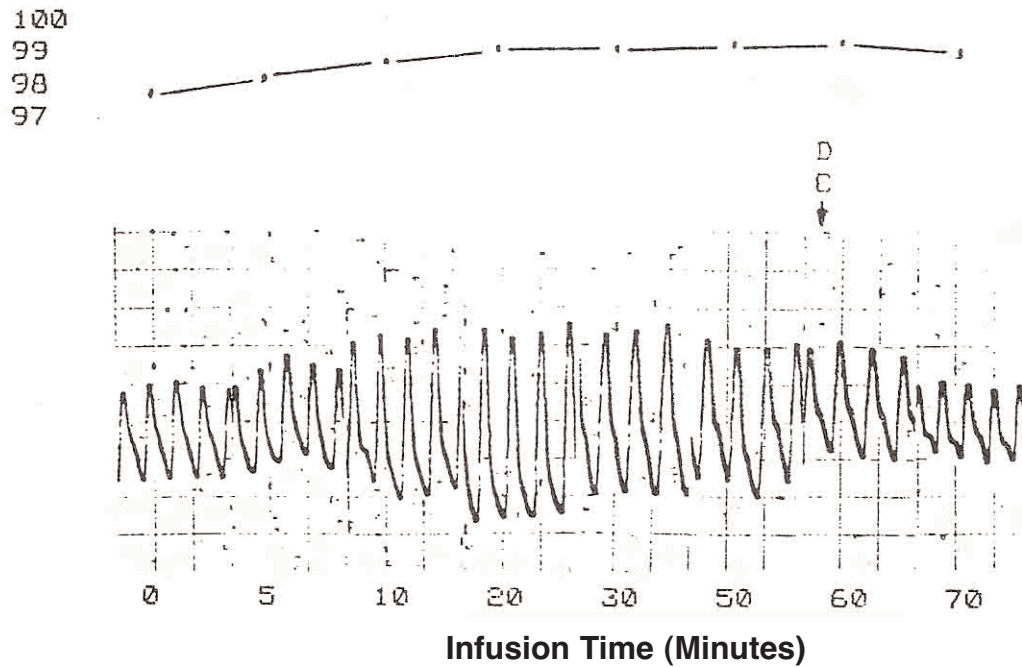


FIGURE 3 (above):

Digit vasodilation and body temperature response to the infusion of 150 ml 0.15% Hydrogen Peroxide in 5% Dextrose in water.

Between 5 and 10 minutes after the beginning of the infusion, an increase in amplitude of the pulse volume patterns is noted with a maximum increase obtained in approximately 15 minutes. A rise in axillary temperature of 1 degree was recorded and corresponds to the increase in metabolic rate previously determined. The increased amplitude of the pulse volume recording indicates vasodilation of the peripheral arterioles has occurred. Both vasodilation and increased temperature remained constant throughout the infusion. The dilated vessels returned to their pre infusion size within 10 minutes after the infusion was discontinued but the temperature returned to the pre-infusion level more slowly. This was probably due to the poor diffusion of heat from the axilla. In another experiment (not illustrated) increased metabolic rate, vasodilation and increased temperature were constant throughout the infusion of 500 ml of 0.15% H₂O₂. Repeated daily infusions of 500 ml for six consecutive days also show a duplicate response throughout each day's infusion.

Part of the clinical benefits observed with the intravenous infusions of H₂O₂ may be due to increased microcirculation as demonstrated in this experiment. The increase in temperature is a function of increased metabolic rate and can be used as a simple clinical method to indicate if the infused H₂O₂ solution is stimulating the oxidative enzyme systems.

Discussion

An increase in metabolic rate, in a resting subject, will not occur unless oxidative enzyme systems are stimulated. The substrate must contain an adequate supply of oxygen and ADP for this increase to be sustained. Since, in these experiments, the subjects did not expend energy, did not increase respiratory effort and the ambient room oxygen did not change, the increase in metabolic rate was due to the effect of infused H₂O₂. In our studies, the average increase (100%) in metabolic rate, from base level, is equal to 2,000 calories per 24 hours. To increase the metabolic rate 2,000 calories, requires 416 liters of oxygen since one liter of oxygen produces 4.825 calories. A constant infusion of 0.15% H₂O₂ over 24 hours would produce 3,456 ml of oxygen or less than 1% of the amount necessary to obtain the results we measured. ***We conclude therefore, the increase in the metabolic rate is due to the stimulation of oxidative enzymes and not to the oxygen produced by the H₂O₂.***

Hothersall⁵² found H₂O₂ activated the pentose phosphate pathway and activity of glutathione peroxidase greatly increased, both increasing metabolic rate. Glutathione peroxidase activity is not stimulated, however in selenium deficiency⁵³. The delay in the reaction of increasing the metabolic rate and pO₂ measurements in tissue after the infusion of H₂O₂ may be partially explained by the studies of Wrigglesworth⁵⁴. He found very low concentrations of hydrogen peroxide formed a stable intermediate complex with oxidized cytochrome c, which existed for up to 30 minutes. Further reduction of this intermediate by H₂O₂ then occurs, indicating cytochrome c oxidase possesses a catalase-like activity. The complex was not formed when higher concentrations of H₂O₂ were employed. Mitochondrial concentrations of H₂O₂, in our test subjects, would be extremely small when the infused H₂O₂ is fully diluted throughout the body.

Polymorphonuclear leukocytes and other inflammatory cells produce small amounts of H₂O₂, hydroxyl and singlet oxygen radicals in response to the appropriate stimuli⁵⁵. A concentration dependent inhibition in the ability of vessels to produce PGI₂ has been identified in studies of vascular arachidonic acid metabolism⁵⁷. PGE₂ and PGF_{2a} were also inhibited in vessel microsomes when exposed to H₂O₂. This suggests H₂O₂ by intravenous infusion should precipitate an inflammatory reaction in the vessel. Polgar et al.⁵⁸, however, found larger concentrations of H₂O₂ increased prostaglandin synthesis in human fibroblast cultures. Hydrogen peroxide produced by ascorbic acid has been shown to induce prostaglandin synthesis^{58,59,60}. This would suggest the beneficial clinical effects observed with the use of ascorbic acid in inflammatory reactions and, its protective action against infections, is acting through the generation of H₂O₂. Also, there is no evidence H₂O₂ initiates or supports microsomal lipid peroxidation⁶¹. This is the opposite of the predicted effect that H₂O₂ will react with transition metals to form hydroxyl radicals which induce lipid peroxidation. Hydrogen peroxide has also been found to modify the kinetic cooperativity of (Na,K)-ATPase⁶² which also contributes to an increase in metabolic rate. There are rate limiting factors in all enzyme systems. We speculate the plateau and 'all-or-none' effects of our test results were produced by rate limiting factors of the stimulated enzyme systems. The intermediate metabolism of H₂O₂ and activation of oxidative enzyme systems will require further investigation.

Clinical Experience

We have given over 500 intravenous infusions of H₂O₂ in a variety of pathological conditions without a singular systemic side effect observed. Initially we had an occasional phlebitis occur at the injection site. This was overcome by injecting 2500 IU of heparin into the vessel immediately prior to infusing the H₂O₂ solution. The H₂O₂ solution is quite acid (pH 4.5) and requires buffering with sodium bicarbonate with further reduces the local inflammatory effect. Acutely ill patients with infection, allergy reactions, flu syndromes and other toxic phenomena had rapid improvement from their morbid state with infusion of H₂O₂ without further treatment.

We attribute this response to oxidation of toxic substances rather than an increase in tissue oxygen.

The results of our experiment demonstrates intravenous infusions of H₂O₂ has a measurable metabolic effect. As speculated by others, the oxygen produced by H₂O₂ diffuses from the pulmonary capillaries (see discussion of patient C.G.) into the alveoli but our experiments indicate it is reabsorbed into the blood. If the diffused oxygen were expired, the pO₂ in the expired air would increase. This would result in our instrument measuring a decrease in metabolic rate instead of the increase which actually occurred.

Whole blood specimens taken before, during and after the infusions showed color changes consistent with oxyhemoglobin formation. The specimen at the completion of the infusion was obviously more crimson in color compared to the pre-treatment specimen. Numerous blood profile and CBC studies were performed before and immediately after infusions of H₂O₂ with and without DMSO. Although early investigators reported no changes in blood elements and certain chemical constituents, except when injected into the carotid arteries, we found consistent changes worthy of note. After the intravenous infusion of 250 ml 0.15% H₂O₂, a 2% to 10% decrease was noted in the following blood constituents: Bun, Sodium, Potassium, Chloride, Uric acid, Calcium, Phosphorus, Total Protein, Total Bilirubin, Alkaline Phosphatase, AST, ALT, GGTP, LDH, Iron and Globulin.

Intra-arterial infusions were reported in earlier studies to cause an increase in cholesterol and cholesterol esters. We recorded, however, a 7% to 15% decrease in both triglycerides and cholesterol. Glucose showed a slight elevation (25%) but this was attributed to the glucose in the carrier solution. Twelve hours after infusion, all measured constituents had returned to their pre-infusion baseline levels. Formed blood elements showed no change in differential count but both total white and red cell counts were constantly reduced by 5% to 10% in repeated studies. There was also a 5% to 10% reduction in hemoglobin and the hematocrit. We were concerned repeated infusions might produce bone marrow depression or anemia. Platelet counts were occasionally elevated. We found, within 12 to 18 hours after the infusion, a physiological rebound occurred and the hemoglobin and hematocrit levels consistently rose to 2% to 5% above the pre-infusion baseline levels. White cells and platelet counts returned to their normal pre-infusion levels. The addition of DMSO to the H₂O₂ solutions did not modify these responses.

Repeated daily intravenous infusions, four days a week for six months in 2 patients, showed no significant changes in any of the blood elements or constituents reported above.

Long term follow up studies are continuing.

Conclusions

Perhaps we have become myopic about biological oxidation!

The majority of investigational studies seem to concentrate on the damaging effects of biological oxidation and the production of free radicals. Hydrogen peroxide is usually treated as an intermediate or by-product of metabolism and considered of minor significance in metabolic pathways except as it relates to biochemical disruption, tissue or cellular damage.

We feel the physiological effects of bio-oxidation and in particular, hydrogen peroxide, should be investigated with a new prospect.

From the 2,500 or more references on hydrogen peroxide we have collected and reviewed, we have come to appreciate this physiological product as an extremely important molecule in metabolism. Hydrogen peroxide is produced by all cells of the body for many different physiological reasons. The granulocytes produce H₂O₂ as a first line of defense against bacteria, yeast, virus, parasites, and most fungi. It is involved in any metabolic pathway which utilize oxidases, peroxidases, cyclo-oxygenase, lipoxygenase, myeloperoxidase, catalase, and probably many other enzymes. Hydrogen peroxide is involved in protein, carbohydrate and fat metabolism, immunity, vitamin and mineral metabolism or any other system you might wish to explore.

Our studies demonstrate a positive metabolic effect to intravenous infusion of H₂O₂. Its ability to oxidize almost any physiological or pathological substance, in addition to producing increased tissue and cellular oxygen tensions, has proven it to have therapeutic value.

We feel the evidence presented should stimulate a new appreciation in the study of the potential therapeutic application of bio-oxidative mechanisms.