On The Mechanisms Of Toxicity Of Chlorine Oxides Against Malarial Parasites - An Overview

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The purpose of this article is to propose research. Nothing in this article is intended as medical advice. No claims, promises nor guarantees are made.

ABSTRACT

Sodium chlorite (NaClO2) can be acidified as a convenient method to produce chlorine dioxide (ClO2) which is a strong oxidant and a potent disinfectant. A protocol has been developed whereby a solution of these compounds can be taken orally. This procedure rapidly eliminates malaria and other infectious agents in only one dose. Chlorine dioxide (ClO2) is highly reactive with thiols, polyamines, purines, certain amino acids and iron, all of which are necessary for the growth and survival of pathogenic microbes. Properly dosed this new treatment is tolerable orally with only transient side effects. More research to better document efficacy in malaria and in other infections is urgently called for.

DISCOVERY

Jim Humble, a modern gold prospecting geologist, needed to travel to malaria infested areas numerous times. He or his coworkers would on occassion contract malaria. At times access to modern medical treatment was absolutely unavailable. Under such dire circumstances it was found that a solution useful to sanitize drinking water was also effective to treat malaria if diluted and taken orally. [1a] Despite no formal medical training Mr. Humble had the innate wisdom to experiment with various dosage and administration techniques. Out of such necessity was invented an easy to use treatment for malaria which was found rapidly effective in almost all cases. [1b,1c]

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MATERIALS AND METHODS

The procedure as used by Mr. Humble follows: A 28% stock solution of 80% (technical grade) sodium chlorite (NaClO2) is prepared. The remaining 20% is a mixture of the usual excipients necessary in the manufacture and stabilization of sodium chlorite powder or flake. Such are mostly sodium chloride (NaCl) ~19%, sodium hydroxide (NaOH) <1%, and sodium chlorate (NaClO3) <1%. The actual sodium chlorite present is therefore 22.4%. Using a medium caliber dropper (25 drops per cc), the usual administered dose per treatment is 6 to 15 drops. In terms of milligrams of sodium chlorite, this calculates out to 9mg per drop or 54mg to 135mg per treatment. Effectiveness is enhanced, if prior to administration the selected drops are premixed with 2.5 to 5 cc of table vinegar or lime juice or 5-10% citric acid and allowed to react for 3 minutes. The resultant solution is always mixed into a glass of water or apple juice and taken orally. The carboxylic acids neutralize the sodium hydroxide and at the same time convert a small portion of the chlorite (ClO2-) to its conjugate acid known as chlorous acid (HClO2). Under such conditions the chlorous acid will oxidize other chlorite anions and gradually produce chlorine dioxide (ClO2). Chlorine dioxide appears in solution as a yellow tint which smells exactly like elemental chlorine (Cl2). The above described procedure can be repeated a few hours later if necessary. Considerably lower dosing should be applied in children or in emaciated individuals scaled down according to size or weight. The diluted solution can be taken without food to enhance effectiveness but this often causes nausea. Drinking extra water usually relieves this. Nausea is less likely to occur if food is present in the stomach. Starchy food is preferable to protein as protein quenches chlorine dioxide. Significant amounts of vitamin C (ascorbic acid) must not be present at any point in the mixtures or else this will quench the chlorine dioxide (ClO2) and render it ineffective. For the same reason antioxidant supplements should not be taken on the day of treatment. Other side effects reported are transient vomiting, diarrhea, headache, dizziness, lethargy or malaise. [2a,2b]

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EXPLORING BENEFITS

I first learned of Jim Humble's remarkable discovery in the fall of 2006. That sodium chlorite or chlorine dioxide could kill parasites in vivo seemed immediately reasonable to me at the onset. It is well known that many disease causing organisms are sensitive to oxidants. Various compounds classifiable as oxides of chlorine such as sodium hypochlorite and chlorine dioxide are already widely used as disinfectants. What is novel and exciting here is that Mr. Humble's technique seems: 1) easy to use, 2) rapidly acting, 3) successful, 4) apparently lacking in toxicity, and 5) affordable. If this treatment continues to prove effective, it could be used to help rid the world of one of the most devasting of all known plagues.

[3a,3b,3c,3d,3e] Especially moving in me is the empathy I feel for anyone with a debilitating febrile illness. I cannot forget how horrible I feel whenever I have caught influenza. How much more miserable it must be to suffer like that again and again every 2 to 3 days as happens in malaria. Millions of people suffer this way year round. 1 to 3 million die from malaria every year mostly children. Thus motivated I sought to learn all I could about the chemistry of the oxides of chlorine. [4a-4hh] I wanted to understand their probable mechanisms of toxicity towards the causative agents of malaria (Plasmodium species). I wanted to check available literature pertaining to issues of safety or risk in human use.

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OXIDANTS AS PHYSIOLOGIC AGENTS

Oxidants are atoms or molecules which take up electrons. Reductants are atoms or molecules which donate electrons to oxidants. I was already very familiar with most of the medicinally useful oxidants. I had taught at numerous seminars on their use and explained their mechanisms of action on the biochemical level. Examples are: hydrogen peroxide, zinc peroxide, various quinones, various glyoxals, ozone, ultraviolet light, hyperbaric oxygen, benzoyl peroxide, anodes, artemisinin, methylene blue, allicin, iodine and permanganate. Some work has been done using dilute solutions of sodium chlorite internally to treat fungal infections, chronic fatigue, and cancer; however, little has been published in that regard. [5a-5h]

Low dose oxidant exposure to living red blood cells induces a change in oxyhemoglobin (Hb-O2) activity so that more oxygen (O2) is released to tissues throughout the body. [6a-6d] Hyperbaric oxygenation (oxygen under pressure) is: 1) a powerful detoxifier against carbon monoxide; 2) a powerful support for natural healing in burns, crush injuries, and ischemic strokes; and 3) an effective aid to treat most bacterial infections. [7a-7d]

Taken internally, intermittently and in low doses many oxidants have been found to be powerful immune stimulants. Sodium chlorite acidified with lactic acid as in the product "WF10" has similarly been shown to modulate immune activation. Exposure of live blood to ultraviolet light also has immune enhancing effects. These treatments work through a natural physiologic trigger mechanism, which induces peripheral white blood cells to express and to release cytokines. These cytokines serve as a control system to down-regulate allergic reactions and as an alarm system to increase cellular attack against pathogens. [8a-8v]

Activated cells of the immune system naturally produce strong oxidants as part of the inflammatory process at sites of infection or cancer to rid the body of these diseases. Examples are: superoxide (*OO-), hydrogen peroxide (H2O2), hydroxyl radical (HO*), singlet oxygen (O=O) and ozone (O3). [9a-9v] Another is peroxynitrate (-OONO) the coupled product of superoxide (*OO-) and nitric oxide (*NO) radicals. [10a-10h] Yet another is hypochlorous acid (HOCl) the conjugate acid of sodium hypochlorite (NaClO). [11a,11b,11c] The immune system uses these oxidants to attack various parasites. [12a,12b,12c]

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OXIDES OF CHLORINE AS DISINFECTANTS

All bacteria have been shown to be incabable of growing in any medium in which the oxidants (electron grabbers) out- number the reductants (electron donors). [13a] Therefore, oxidants are at least bacteriostatic and at most are bacteriocidal. [13b] Many oxidants have been proven useful as antibacterial disinfectants. [13c,13d] Hypochlorites (ClO-) are commonly used as bleaching agents, as swimming pool sanitizers, and as disinfectants. At low concentrations chlorine dioxide (ClO2) has been shown to kill many types of bacteria [14a-14j], viruses [15a-15L] and protozoa [16a-16f]. Ozone (O3) or chlorine dioxide (ClO2) are often used to disinfect public water supplies or to sanitize and deodorize waste water. [17a-17L] Sodium chlorite (NaClO2) or chlorine dioxide (ClO2) solutions are used in certain mouth washes to clear mouth odors and oral bacteria. [18a-18i] Chlorine dioxide sanitizes food preparation facilities. [19a] Acidified sodium chlorite is FDA approved as a spray in the meat packing industry to sanitized meat. [20a-20g] This can also be used to sanitize vegetables and other foods. [21a,21b] Farmers use this to cleanse the udders of cows to prevent mastitis, [22a,22b,22c] or to rid eggs of pathogenic bacteria. Chlorine dioxide can be used to disinfect endoscopes. [23a] Oxidants such as iodine, various peroxides, permanganate and chlorine dioxide can be applied topically to the skin to treat infections caused by bacteria or fungi. [24a-24d]

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MALARIA IS OXIDANT SENSITIVE

From November 2006 through May of 2007 I spent hundreds of hours searching biochemical literature and medical literature pertaining to the biochemistry of Plasmodia. Four species are commonly pathogenic in humans namely: Plasmodium vivax, Plasmodium

falciparum, Plasmodium ovale and Plasmodium malariae. What I found was an abundance of confirmation that, just like bacteria, Plasmodia are indeed quite sensitive to oxidants. [25a-25p]. Examples of oxidants toxic to Plasmodia include: artemisinin, artemether [26a-26n], t-butyl hydroperoxide [27a], xanthone [28a], various quinones [29a-29m] (e.g. atovaquone, lapachol, beta-lapachone, menadione) and methylene blue [30a-30i].

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TARGETING THIOLS

Like bacteria, fungi and tumor cells, the ability of Plasmodia to live and grow depends heavily on an internal abundance of reductants. This is especially true regarding thiol compounds also known as sulfhydryl compounds (RSH). [31a,31b] Thiols as a class behave as reductants (electron donors). As such they are especially sensitive to oxidants (electron grabbers). Thiols (RSH) such as glutathione [32a-32L] and other sulfur compounds [33a,33b,33c] are reactive with sodium chlorite ($NaClO_2$) and with chlorine dioxide (ClO_2). These are the very agents present in Mr. Humble's solution. The products of oxidation of thiols (RSH) using various oxides of chlorine are: disulfides (RSSR), disulfide monoxides (RSSOR), sulfenic acids (RSOH), sulfinic acids (RSO_2H), and sulfonic acids (RSO_3H). None of these can support the life processes of the parasite. Upon sufficient removal of the parasite's life sustaining thiols by oxidation, the parasite rapidly dies. [34a-34e] A list of thiols (RSH) upon which survival of Plasmodium species heavily depend includes: lipoic acid and dihydrolipoic acid [35a-35h], coenzyme A and acyl carrier protein [36a-36f], glutathione [37a-37m], glutathione reductase [38a-38e], glutathione-S-transferase [39a-39g], peroxiredoxin [40a-40L], thioredoxin [41a-41g], glutaredoxin [42a,42b,42c], plasmoredoxin [43a], thioredoxin reductase [44a-44g], falcipain [45a-45i], and ornithine decarboxylase [46a-46e].

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HEME IS AN OXIDANT SENSITIZER

Of particular relevance to treating malaria is the fact that Plasmodial trophozoites living inside red blood cells must digest hemoglobin as their preferred protein source. [47a,47b] They accomplish this by ingesting hemoglobin into an organelle known as the "acid food vacuole". [47c-47h] Incidently, the high concentration of acid in this organelle could serve as an additional site of conversion of chlorite (ClO2-) to the more active chlorine dioxide (ClO2) right inside the parasite. Furthermore, Plasmodia consume 50 to 100 times more glucose than noninfected red blood cells most of which is metabolized to lactic acid a known activator of chlorite. [48a-48b]

Next falcipain (a hemoglobin digesting enzyme) hydrolyzes hemoglobin protein to release its nutritional amino acids. [49a-49e] A necessary byproduct of this digestion is the release of 4 heme molecules from each hemoglobin molecule digested. Free heme (also known as ferriprotoporphyrin IX) is redox active and can react with ambient oxygen (O2), an abundance of which is always present in red blood cells. This produces superoxide radical (*OO-), hydrogen peroxide (H2O2) and other reactive oxidant toxic species (ROTS). [50a-50bb]. These can rapidly poison the parasite internally. To protect themselves against this dangerous side-effect of eating blood protein, Plasmodia must maintain a high reductant capacity (an abundance of reduced thiols and NADPH) to quench these ROTS. This is their main mechanism of antioxidant defense. [51a-51n]

Plasmodia must also rapidly and continuously eliminate heme , which is accomplished by two methods. 1) heme is polymerized producing hemozoin. [52a-52k] 2) heme is metabolized in a detoxification process that requires reduced glutathione (GSH). [53a,53b] Therefore any method (especially exposure to oxidants) which limits the availability of reduced glutathione (GSH) will cause a toxic build up of heme and of ROTS inside the parasite cells. Sodium chlorite and chlorine dioxide (the exact agents present in Mr. Humble's treatment) readily oxidize glutathione. [54a,54b] Therefore, a rapid killing of Plasmodia upon taking acidified sodium chlorite orally should be expected.

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OVERCOMING ANTIBIOTIC RESISTANCE WITH OXIDATION

Now the issue of resistance of Plasmodium species to commonly used antiprotozoal antibiotics must be addressed. Quinine, chloroquine, mefloquine, quinacrine, amodiaquine, primaquine and other quinoline-like antibiotics all work by blocking the heme detoxifying system inside the trophozoites. [55a-55gg] Many Plasmodial strains against which quinolines have repeatedly been used have found ways to adapt to these drugs and to acquire resistance. Research into the mechanisms of resistance has found that often resistance is accomplished by a meere upregulation of glutathione production and utilization. [56a-56j] Consequently oxidizing or otherwise depleting glutathione inside the parasite usually restores sensitivity to the quinoline antibiotics. [57a-57f] Therefore, protocols combining the use of oxidants with quinolines are under developement and already showing signs of success. [57g] In this context let us consider that no amount of intraplasmodial glutathione (GSH) could ever resist exposure to a suffient dose of chlorine dioxide (ClO_2). Note that each molecule of ClO_2 can disable 1 to 5 molecules of glutathione depending on the reaction mechanism.

$2(GSH) + 2(ClO_2) \rightarrow 1(GSSG) + 2(H^+) + 2(ClO_2^-)$
or $10(GSH) + 2(ClO_2) \rightarrow 5(GSSG) + 2(H^+) + 2(Cl^-) + 4(H_2O)$

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SOME INCOMPATIBILITIES

Acidified sodium chlorite could provide a powerful new opportunity to improve or to restore sensitivity to quinolines by virtue of its oxidative power. However, quinolines contain secondary or tertiary amino groups which react with chlorine dioxide in such a way that both could destroy each other. Some possible strategies to resolve this incompatibility are suggested below.

1. Acidified sodium chlorite could be used as explained above only as a solo therapy.
2. Quinoline administration could be withheld until after the acidified sodium chorite has completed its action.
3. Patients already preloaded with a quinoline could stop this, wait a suitable period of time for this to wash out, then administer the acidified sodium chlorite.
4. The quinoline could remain in use and while the less active sodium chlorite is administered without acid. This should retain plenty of oxidant effectiveness without destroying any quinoline or wasting too much oxidant.
5. Switch from a quinoline to an endoperoxide (such as artemisinin) or to a quinone (such as atovaquone) before using acidified sodium chlorite, as these may be less sensitive toward destruction by chlorine dioxide.

Similar problems apply to methylene blue and many other drugs if they have an unoxidized sulfur atom, a phenol group, a secondary amine or a tertiary amine. Such are also very reactive with the chlorine dioxide component. [58a]

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REDUCTANT RECOVERY SYSTEMS

Living things possess a recovery system to rescue oxidized sulfur compounds. It operates through donation of hydrogen atoms to these compounds and thereby restores their original condition as thiols. [59a,59b]

2 [H] + (GSSG) -> 2(GSH)

This system is known as the hexose monophophate shunt. [59c,59d] A key player in this system is the enzyme glucose- 6-phosphate-dehydrogenase (G6PDH). Patients with a genetic defect of G6PDH, known as glucose-6-phosphate-dehydrogenase deficiency disease, are especially sensitive to oxidants and to prooxidant drugs. However, this genetic disease has a benefit in that such individuals are naturally resistant to malaria. They can still catch malaria, but it is much less severe in them, since they permanently lack the enzyme necessary to assist the parasite in reactivating glutathione and other oxidized thiols. [60a-60i] Chlorine dioxide (ClO2) has been shown to oxidize and denature G6PDH by reaction with tyrosine and tryptophan residues inside the enzyme. [61a] Furthermore, G6PDH is sensitive to inhibition by sodium chlorate (NaClO3), another member of the chlorine oxide family of compounds. [61b,61c,61d] Sodium chlorate (NaClO3) is a trace ingredient present in Jim Humble's antimalarial solution. Some sodium chlorate (NaClO3) should also be produced in vivo by a slow reaction of chlorine dioxide (ClO2) with water under alkaline conditions [61e].

2(ClO2) + 2(OH-) -> (ClO2-) + (ClO3-) + H2O

The Plasmodia may attempt to restore any thiols (RSH) lost to oxidation. However, this becomes more difficult as G6PDH is inhibited by chlorine dioxide (ClO2) or by chlorate (ClO3-).

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TARGETING IRON

While most available literature refers to redox imbalances causing depletion of necessary thiols. Other mechanisms of toxicity of the oxides of chlorine against Plasmodia should also be considered. Oxides of chlorine are generally rapidly reactive with ferrous iron (Fe++) converting it to ferric (Fe+++). [62a-62d] This explains why in cases of overdosed exposures to oxides of chlorine such as sodium chlorite ($NaClO_2$) there was a notable rise in methemoglobin levels. [63a,63b] Methemoglobin is a metabolically inactive form of hemoglobin in which its ferrous iron (Fe++) cofactor has been oxidized to ferric (Fe+++). In living things including parasites iron is a necessary cofactor for many enzymes. [64a-64f] Thus it is reasonable to expect that any damage to Plasmodia caused by oxides of chlorine is compounded by conversion of ferrous (Fe++) cofactors to ferric (Fe+++) or other alterations of iron compounds. [65a-65g] Superoxide dismutase (SOD) inside Plasmodial cells also utilizes iron in its active center. [66a-66m] Chlorine dioxide also oxidizes manganese. [67a]

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TARGETING POLYAMINES

Other metabolites necessary for survival and growth in tumors, bacteria and parasites are the polyamines. [68a-68d] Plasmodia quit growing and die, when polyamines are lacking [69a-69k], or when their functions are blocked [70a-70L]. Polyamines are also sensitive to oxidation and can be eliminated by strong oxidants. When oxidized, polyamines are converted to aldehydes, which are deadly to parasites and to tumors. [71a-71e] Chlorine dioxide (ClO2) is known to be especially reactive against secondary amines. [72a] This includes spermine and spermidine the two main biologically important polyamines. Thus any procedure which is successful to oxidize both thiols and polyamines does quadruple damage to the pathogen: 1) oxidation of the thiol ornithine decarboxylase inhibits polyamine synthesis; 2) oxidation of the thiol S-adenosyl-L-methionine decarboxylase also inhibits polyamine synthesis; (see references below and in "Targeting Thiols" above) 3) oxidation of the secondary amines spermidine and spermine depletes polyamine supplies; 4) the products of polyamine oxidation are toxic aldehydes.

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TARGETING PURINES

Purines are essential to many life processes. These molecules have a double ring structure. The rings are heterocyclic being composed of both carbon and nitrogen. Their nitrogen atoms are vulnerable to reaction with chlorine dioxide. [73a] Examples of important biologic purines are xanthine, hypoxanthine, inosine, guanine and adenine. Guanine and adenine are essential components of DNA and RNA necessary for all genetic functions and for all protein syntheses. Adenine is an essential component of the cofactors NADH, NADPH, FAD and ATP, necessary for many metabolic functions including oxidation-reduction and energy metabolism. Any purines lost by chlorine dioxide exposure can be readily replaced by host cells. [74a] Plasmodia and other apicomplexae are uniquely vulnerable to purine deficiency as they lack the enzymes necessary to produce purines for themselves [75a,75b,75c]. Instead these must be scavenged from host cells and imported across the plasma membranes of the parasite cells. [76a-76i] Drugs are under development to inhibit purine utilization by Plasmodia and are already showing signs of success. [77a-77g] Temporarily destroying some of the purines in the blood as should occur upon brief exposure to chlorine dioxide in vivo is probably an additional stress that Plasmodia cannot tolerate.

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TARGETING PROTEINS

Chlorine dioxide (ClO_2) is highly reactive with thiols, phenols, secondary amines and tertiary amines. Therefore, proteins composed of amino acids which present these reactive groups are vulnerable to oxidation by this agent. Proteins which present residue(s) of the amino acid L-cysteine are discussed above under TARGETING THIOLS. L-tyrosine presents a phenol group and is therefore similarly vulnerable. L-tryptophan and L-histidine present secondary amino groups which are also especially reactive with chlorine dioxide. [78a-78d]

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SAFETY ISSUES

A remaining concern is safety. So far, at least anecdotally, the dosages of chlorine oxides as administered orally per Jim Humble's protocol have produced no definite toxicity. Some have taken this as often as 1 to 3 times weekly and on the surface seem to suffer no ill effects. To be certain if this is safe more research is warranted for such long term or repeated use. The concern is that too much or too frequent administration of oxidants could excessively deplete the body's reductants and promote oxidative stress. One useful way to monitor this may be to periodically check methemoglobin levels in frequent users. Sodium chlorite, as found in municipal water supplies after disinfection by chorine dioxide, has been studied and proven safe. [79a-79j] Animal studies using much higher oral or topical doses have proven relatively safe. [80a-80t] In a suicide attempt 10g of sodium chlorite taken orally caused nearly fatal kidney failure and refractory methemoglobinemia. [81a] Inhalation or aerosol exposure to chlorine dioxide gas is highly irritating and generally not recommended. [82a-82g] Special precautions must be employed in cases of glucose-6- phosphate-dehydrogenase deficiency disease, as these patients are especially sensitive to oxidants of all kinds. [83a-83g] Nevertheless, oral acidified sodium chlorite solutions might even be found safe [84a,84b] and effective in them, but probably will need to be administered at lower doses.

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MORE RESEARCH

It is hoped that this overview will spark a flurry of interest, and stimulate more research into the use of acidified sodium chlorite in the treatment of malaria. The above appreciated observations need to be proven more rigorously and published [85a]. The biochemistry most likely involved suggests that other members of the phylum Apicomplexa should also be sensitive to this treatment. [86a] This phylum includes: Plasmodium, Babesia, Toxoplasma [87a], Cryptosporidium [88a], Eimeria, Theileria, Sarcocystis, Cyclospora, Isospora and Neospora. These pathogens are responsible for widespread diseases in humans, pets and cattle. Other thiol dependent parasites should also be susceptible to acidified sodium chlorite. For example Trypanosoma and Leishmania extensively utilize and cannot survive without the cofactor known as trypanothione. Each molecule of trypanothione presents 2 sulfur atoms and 5 secondary amino groups all of which are vulnerable to oxidative destruction from chlorine dioxide (ClO2). [89a-89p]

Chlorine dioxide has been proven to be cidal to almost all known infectious agents in vitro using remarkably low concentrations. This includes parasites, fungi, bacteria and viruses. The experiences noted above imply that this compound is tolerable orally at effective concentrations. [90a,90b] Therefore extensive research is warranted to determine if acidified sodium chlorite is effective in treating other infections. We may be on the verge of discovering the most potent and broad spectrum antimicrobial agent yet known. Special thanks go to Jim Humble for his willingness to share his discovery with the world.

by Thomas Lee Hesselink, MD

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