ANTHROPOLOGY PROGRAM
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Dear Dr Lederberg,

I would like to tell you about a new research project and conference that is hoped will assist in developing a solution to the problem of infectious disease treatment in an age of antibiotic and multiple drug resistance (and please excuse the length of this unsolicited letter, but I hope you will find it of value). The project and upcoming conference are based on preliminary research which indicates that a particular form of hyperthermia appears to be as or more effective than antibiotics in treating a number of infectious organisms, including, according to preliminary indications, *Staphylococcus aureus*. A second line of research, carried out by scientists from Rockefeller, Yale, and several other universities and institutions, including the Max Planck Institute, has demonstrated that a form of hyperthermia which possesses the same properties as that used effectively against a number of micro-organisms in the laboratory can be produced, perhaps surprisingly, through a set of behavioral medicine techniques. According to our initial data and analysis, induction and maintenance of a "mild" or fever-like hyperthermia effect for a specific duration (roughly from one to several hours) at the site of an infectious challenge, can lead to the enhancement of the oxygen-dependent antimicrobial capacity of phagocytic cells (Knighton et al 1986; Kurz et al 1996; Von Furth and Van den Berg 1996; Allen et al 1997), the production of immune-augmenting cytokines (Downing et al 1988; Hasday 1997), and enhancement of the performance of the natural killer (NK) cell system (Downing et al 1988; Burd et al 1998), with potentially substantial and medically important microbicidal effects, unanticipated by previous researchers.

The behavioral medicine research of the Rockefeller University and other scientists follows in a distinguished historical lineage that derives from Pavlov and from the North American behaviorist tradition developed by Skinner and others, and demonstrates that individuals may learn to achieve "acquired (voluntary) control of peripheral vascular responses" (Lynch and Schuri 1977; Miller 1989) through the development of an integrated set of self-conditioning, somatosensory discrimination, and other behavioral techniques. These researchers found that techniques consisting of focused attention to heat-related cognitions (efferent function) could, with practice, lead further to an actual rise in temperature, through activation of the corticofugal-peripheral nervous system

pathways controlling vasomotor tone (Kunzendorf 1990; Kojo 1985, 1990; Lynch and Schuri 1977). The initial modest changes could be perceived (afferent function) and amplified, with or without the aid of technical feedback devices (ie, "biofeedback"; Miller 1989; Kojo 1985, 1990; Piedmont 1981), to a level within the upper physiologic or febrile range (approximately 37 to 40 degrees C). Although this latter line of research was *not* specifically designed to investigate the use of behavioral hyperthermia-inducing techniques for prevention or treatment of infection, my colleagues and I have begun to synthesize the results of this research with other very recent clinical and microbiological studies on the potentially powerful microbicidal effects of hyperthermia.

How exactly would these vasomotor and consequent temperature changes mediate *microbicidal* effects? Briefly, our analysis, based on direct and indirect evidence, from in vitro and in vivo studies on animals and humans, indicates the following. Moderate, febrile hyperthermia significantly increases the oxygen available for phagocytic cells, which often falls below critical levels (ie, below approximately 40 mm Hg) in the hypoxic microenvironments of wounds and sites of infections (Knighton et al 1984, 1986, and references therein). Increases in tissue oxygen tension which can be induced through hyperthermia have been found to enhance microbicidal performance to the extent of producing an antibiotic effect *equivalent to or greater than* that provided by standard antibiotic medication (eg, ampicillin), in studies directly comparing the two treatment conditions (Knighton et al, "Oxygen as an Antibiotic: A Comparison of the Effects of Inspired Oxygen Concentration and Antibiotic Administration on In Vivo Bacterial Clearance," Archives of Surgery, 1986; also Knighton et al 1984; Rabkin & Hunt 1987; in these studies it was found that by increasing local temperature to an average 38.0 degrees C for an average of 42 minutes it was possible to achieve the same increase in oxygen tension, of between 20 and 40 mm Hg, produced by the increased oxygenation responsible for the antibiotic effect).

Furthermore, the same magnitude and duration of temperature increase has been found to enhance the recruitment, migration, and cytokine expression of NK cells substantially (for example, in one study such a temperature increase raised the level of interferon synthesis 10-fold (Downing et al 1988; Hasday 1997). Recent research has shown that a variety of "activating factors" – including inflammatory substances released at the site of an infectious challenge (such as the superantigen staphylococcus enterotoxins), cytokines, and *heat* – may not only significantly up-regulate NK cytolytic function, but substantially "expand [its] target cell repertoire" as well (D'Orazio & Stein-Streilein 1989; Salazar-Mather et al 1996; Robertson & Ritz 1990). Moreover, NK cells also secrete cytokines that may in turn significantly up-regulate other immune cells, including macrophages (Herberman 1985; Gomez et al 1985) and neutrophils (Klempner et al 1979). Such experiments involving activating factors have led to fundamental revisions in the understanding of the role of the NK cell in the immune system (Whiteside & Herberman 1990), and research in progress right now is identifying the potentially extremely important role that hyperthermia can play as an NK-activating factor, with respect to a previously unsuspected wide range of diseases and pathogenic conditions (eg, Burd et al 1998; Bushell et al, in preparation).

Indeed, the new emerging understanding of the significance and mechanisms of "the NK system" (Whiteside & Herberman 1990) are reflected in the recent spate of studies showing the potentially important and even critical role of the system in host defense against a previously unsuspected wide range of diseases. These include a variety of diseases produced by bacterial pathogens (Garcia-Penarrubia 1991; Greenberg 1989), possibly including *S aureus* (D'Orazio & Stein-Streilein 1996), and mycobacteria, including *mycobacterium avium* (Bermudez & Young 1991), and even tuberculosis (Ratcliffe et al 1994; Bushell et al, in preparation; and see below); parasitic disease, including leishmaniasis (Maasho et al 1998) and schistosomiasis (Wynn et al 1994); and fungal infection (Murphy 1989) as well as viral diseases such as HIV/AIDS (Chehimi et al 1992). And, since the behavioral techniques for inducing "moderate" hyperthermia, presently to be described, appear to provide a superior form of "heat delivery system," it is reasonable to hypothesize that such techniques may stimulate and augment NK system function with potentially clinically significant effects. In fact, preliminary research on the use of such techniques in the treatment of pulmonary tuberculosis – one of the few instances in which such techniques have been formally utilized in the treatment of infectious disease – found, in several detailed case studies, the resolution of symptoms, including cavitation, associated with behaviorally-induced "hyperemia" of the lungs, which were confirmed radiologically (Luthe 1963; see also Linden 1990). In light of the fact that NK cells produce a powerful and rapidly-acting macrophage activating factor (which was tested on alveolar macrophages; Gomez et al 1985; Greenberg 1989; Robertson & Ritz 1990; Bermudez & Young 1991), as well as other relevant cytokines, we are considering the possibility of further research into this enticing subject (see below).

Other significant antimicrobial effects of moderate hyperthermia also include, of course, its limiting effects on the replication of a number of organisms, including certain gram-negative bacteria, parasites such as leishmania, and many viruses (Cunha 1998; Davis & Phair 1997; Navin et al 1990).

Several different behavioral techniques have been found that generate the temperature changes necessary to produce a hyperthermia effect of the same magnitude used effectively for microbicidal purposes, including biofeedback (French et al 1973) and the use of focused states of absorption (Benson et al 1982), but there is a common denominator to the techniques, one that involves the use of heat cognitions, particularly the multisensory imagery of warmth (Bushell et al, in preparation). The heat cognitions apparently trigger a centrifugal cortical-subcortical pathway linked to peripheral sympathetic and parasympathetic fibers which control vasomotor tone (Kunzendorf 1990; Kojo 1985, 1990; Lynch and Schuri 1977). Experimental research into the psychophysics of thermal sensation have shown that changes in local temperature as miniscule as 0.0017 degrees C/sec can be sensed by subjects in experimental research (Hensel 1973, 1981; Kojo 1990), and both the magnitude and locus of temperature change can thereby be consciously regulated according to this incoming information (within limits).

The results can be surprisingly impressive with respect to the agility, dexterity, precision, and power of the behaviorally-mediated temperature regulating system, in terms of the

range of local (and regional) temperature variables potentially accessible to conscious control. In the words of the Rockefeller University researchers, who provide a comprehensive and detailed summary of a body of research into the phenomenon of behavioral control of temperature:

[In one representative study]...19 out of 21 individuals learned increases or decreases in hand temperature in four to six training sessions of 15 minutes each.... [and] (1) most subjects learn with as little as one hour of practice; (2) many subjects can increase or decrease temperature at "will" and can transfer the body locus of temperature change with little decrement in performance once training is complete; (3) feedback is needed only during the early stages of training [but see below]; (4) with extended practice, the locus of control is gradually reduced to the location of the transducer responsible for feedback; (5) retention is nearly perfect after four to five months without practice; (6) control of variations in temperature as great as 9.86 degrees C (17.75 degrees F) are possible....

To this list of impressive features can be added still others: substantial temperature increases can be generated through such behavioral techniques rapidly, such as 10 to 15 degree F increases within 1-2 minutes (Sargent et al 1972; Miller 1975; Schwartz 1984); increases as great as 26 degrees F, and up to 104 degrees F, have been reported in the literature (Schwartz 1984); subjects can maintain stable increases for considerable periods (Taub 1977), including for over several hours (Benson et al 1982), and while simultaneously engaged in other tasks (Benson et al 1982; Taub 1977); feedback from special technical devises are in many cases not necessary, and may even interfere with acquisition of the skill (Miller 1989; Kojo 1985, 1990; Piedmont 1981; Engel 1986); the techniques can apparently produce temperature increases over most cutaneous and superficial tissues that have been tested, including arms, legs, hands, feet, digits, forehead, earlobes, mouth, and trunk (Taub 1977; Benson et al 1982), and deep tissues, including at least several visceral organs (eg, kidney, colon, lungs), are also accessible (Miller 1969, 1975, 1989; Luthe 1963, 1969; Ikemi et al 1965, 1966); children appear to be particularly adept at acquiring the skills (Lynch, Hama, Kohn, & Miller 1976).

The question of course naturally arises: if "moderate" hyperthermia does indeed possess a significant microbicidal potential, then why is this knowledge not more widespread and developed? There are at least several reasons for this. In the first place, as you and others have pointed out, the antibiotic revolution in infectious disease medicine has essentially eclipsed other frameworks and approaches to the subject. Unfortunately, as you and others have also pointed out, this one-sided orientation has, to indulge a metaphor, generated its own "germs" of destruction, in that its exclusivity has left us under-prepared for the emergence of MDR infectious organisms. Secondly, the development of a viable and effective heat delivery system for therapeutic hyperthermia has been significantly hampered by formidable technical problems, which some researchers have summed up with the phrase "the biology is with us but the physics is against us": problems with focusing applied heat with precision, differences in the conductance properties of adjacent tissues, problems with development of noninvasive thermometry, and side effects such as acute discomfort, pain and even tissue damage, have all contributed to what is in many ways a veritable technological impasse (Myerson et al 1997; Seegenschmiedt & Vernon 1995; Navin et al 1990; Neva et al 1984). (A third reason for the relative lack of interest in hyperthermia as an anti-microbial treatment modality, I

believe, is based on the fact that many medical researchers are not familiar with the very recent research demonstrating its potential as a significant stimulatory agent for natural immune system function, including in particular the NK system, as discussed above).

It is perhaps surprising, then, that what appear to be correctives for such "high tech" problems would come from the domain of behavioral medicine. However, as the Rockefeller University researchers emphasize in their comprehensive and detailed reviews of studies on the behavioral control of vasomotor function, blood flow, and temperature, the techniques can produce changes characterized by precision and "specificity" (Miller 1975) in terms of both magnitude and anatomical location, dexterity, and prolonged stability, if desired, and can be successfully directed to deep as well as superficial tissues, learned rapidly, etc.

Perhaps even more surprising is the fact that the potential anti-microbial properties of such behavioral techniques apparently *have been* exploited for some time, particularly by several cultures that possess what might be thought of as highly developed, sophisticated systems of "traditional behavioral medicine." These cultures, including India, China, and Tibet, possess long-standing traditions of "behavioral medicine" which have explicitly considered behaviorally-generated heat as a form of medicine, to be used therapeutically, including specifically against infectious disease (eg, Clifford 1984). Moreover, the ability to generate heat with precision, dexterity, and prolonged stability (ie, for as long as several hours), has been strikingly demonstrated in a study of Tibetan practitioners of a particular form of heat-producing behavioral technique, a study which was conducted by Herbert Benson and colleagues from Harvard Medical School (Nature 295: 234-6, 1982; although the study was not concerned with the use of the technique for infection-fighting purposes).

Because of the exciting and compelling nature of the above evidence, and because of the re-emerging problem of MDR pathogens, my colleagues and I decided to attempt to initiate a program devoted to this multifaceted subject, one that would integrate research and conference interaction between colleagues. In this endeavor I have been joined by Dr Thomas K Hunt, Professor of Surgery and Director of the Wound Healing Laboratory, University of California at San Francisco Medical Center, who is one of the original (post-WWII) pioneering investigators into the role of temperature and oxygen in host defenses against wound-infecting organisms; Dr Ronald B Herberman, Director of the Cancer Institute, University of Pittsburgh, who is the actual discoverer of the NK cell, and who has conducted a sizeable body of research into both the anti-neoplastic and anti-microbial (eg, Levy SM, RB Herberman, et al 1991) properties of the NK system; and Dr N Herbert Spector, former director of labs and programs at the Walter Reed Institute, NSF, and NIH, who has been credited as one of the founders of the field that investigates immune and nervous system interactions (American College of Allergy and Immunology News, November 1993) for his pioneering early experiments that established a connection between the hypothalamus and certain immune variables (Spector et al 1974, 1975), as well as other achievments (Spector et al 1995; Spector 1996, 1997). And, furthermore, because of the evidence for the use of behaviorally-induced hyperthermia

for microbicidal purposes in the Indo-Tibetan tradition, we sought and fortunately obtained the formal participation of the Dalai Lama of Tibet in our project. The Dalai Lama is a leader in cross cultural dialogue, as well as in the dialogue between modern Western science and information systems found in other traditions and cultures, as evidenced by his past participation in conferences with medical and neuroscientists at Harvard Medical School, MIT, and the Centre Nationale de la Recherche Scientifique in Paris.

Based on that conference and other preliminary and follow-up work, we are in the process of designing several studies. In one we will be investigating the potential microbicidal effect of the hyperthermia-generating behavioral medicine techniques against *S aureus*, through a methodology that will be employing skin chamber assays, and subcutaneous oxygen and temperature monitoring. This study is directly tied to one of Hunt's studies, just getting underway, which will be investigating the possible development of resistance to oxygen-based killing mechanisms in *S aureus*. In another study, which is still in initial stages, we hope to investigate the potential effects of the techniques against tuberculosis, which follows on work already done some time ago in Germany (see above). These studies are attempts to answer the call issued by a number of infectious disease specialists (eg, Kernodle and Kaiser 1995, 1997; Ratcliffe et al 1994) for the investigation and development potential "immunostimulatory agents" in the battle against dangerous antibiotic resistant pathogens.

We also currently wish to plan our next conference. We would be greatly honored if you would consider participating in our conference. We would be more than happy to schedule it to accommodate your busy schedule (as well as the schedule of the Dalai Lama, of course). Likewise we would be greatly honored and grateful if you would consider offering any opinions, information, feedback, etc, regarding the development of our conference or research program.

Again, I would like to apologize for the length of this unsolicited letter, and for any undue repetition of information familiar to you. Nevertheless, I hope you will have found it of some value. We look forward to hearing from you at your earliest convenience.

Sincerely,

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