The Antisecretory, Analgesic and Gastrointestinal Healing Properties of Sangre De Grado Reflect a Common Mechanism – Vanilloid Receptor Antagonism

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Introduction

Sangre de grado is a medicinal treasure from Amazonia, but its effectiveness for a diversity of conditions has not been well appreciated in the developed world nor utilized for health maintenance. The reasons for this lie in a lack of knowledge as to how it works, as well as a general poor understanding of Amazonian medicinal plants per se. These problems can be resolved by research and information dissemination of. The value of Amazonia's medicinal plants are often maligned by reiteration of substandard and preliminary research, inappropriate and unsubstantiated claims and influence of commercial entities. We need objective evaluations and responsible reporting of applications, actions and therapeutic possibilities.

Sangre de grado: Ethnomedical Background

Derived from several Croton species (*Croton dracanoides, Croton palanostigma, Croton lechleri*), Sangre de grado is readily available in the Amazon, with the highest quality originating in the Upper Jungle of Peru and Ecuador. The tree is fast growing, reaching heights of 40 feet in three years. Current experimental farming techniques are focusing on growing and felling the trees in a 2-3 year cycle. At this time a tree will have grown to a height of 20-30 feet and produce approximately 1.5 liters of sap; a large quantity considering that Sangre de grado is applied drop by drop. Sangre de grado is best cultivated with other plants; as a stand alone crop it is ravaged by pests, retarding the growth and health of the Croton tree.

Sangre de grado is utilized for a diverse array of conditions (1-4), but we believe there are common mechanistic threads that weave these applications together. Sangre de grado is applied topically to wounds or insect bites and stings to promote healing and as a fast acting analgesic agent. The sap binds to wounds and forms a long lasting seal not that dissimilar to a natural scab. Its inherent antimicrobial activity limits infection. It's other anti-inflammatory actions allows for healing that is devoid of irritating symptoms. Whether these anti-inflammatory actions accelerates healing is not clear, but is a tenable hypothesis. Sangre de grado is also consumed orally, highly diluted, for the treatment of severe gastrointestinal distress (1-4). This includes healing gastrointestinal ulcers, diarrhea and generalized cramping and discomfort. The validity of these gastrointestinal applications have been confirmed by us and Shaman Botanicals (5-7). Sangre de grado has also been used for antiviral activity, as well as for cancer applications. The cancer applications, while evident throughout Amazonia, has been one of the least studied applications by Western scientists, and is the basis of our current investigations. Interestingly, it may have a chemical commonality with its analgesic properties.

Sangre de grado: Proposed Active Chemicals

Over 90% of the chemicals in Sangre de Grado are proanthocyandins, which are largely responsible for the color of the sap. Proanthocyandins are antioxidants, which polymerize into short oligomers (8,9). A variety of proanthocyandins oligomers derived from Sangre de grado, have been patented by Shaman Pharmaceuticals, now doing business as Shaman Botanicals. This company also confirmed that Sangre de grado is an effective treatment for diarrhea. They propose inhibition of cAMP mediated epithelial secretion as the mechanism (6). In contrast, our studies indicate Sangre de grado inhibits epithelial secretion primarily via antagonism of sensory afferent nerves in the gut (7), and that the antisecretory actions of proanthocyandins are too weak to account for this activity.

While proanthocyandins are the major chemical class present in Sangre de grado, there are a number of other chemicals that have been isolated and may be involved in the diverse effects exhibited by Sangre de grado. Phillipson (8,9), noted the presence of crolechinol, crolechinic acid, korberin A and B, 3'4'-O-dimethylcedrusin and taspine have received the most attention, albeit there are only a few studies evaluating this herbal medicine. 3'4'-O-dimethylcedrusin and the polyphenolic fraction have been suggested to be the chemicals responsible for wound healing via an action on fibroblasts (10,11). This cicatrizant effect is perhaps better explained by the array of chemicals acting in concert rather than a single chemical. For example, beyond the antiviral actions of proanthocyanidins, antimicrobial actions may be critical, an effect thought to be due to 1,3,5 trimethoxybenzene and 2,4,6 trimethoxyphenol that are present in trace amounts, but are 30 times more potent than penicillin (8,9). Taspine is present in Peruvian sap, but not from Ecuadorian sap, and has been implicated in its use in inflammation and cancer as it readily kills tumor cells (12,13). In cell culture studies Sangre de grado inhibits cell proliferation, yet protects against cell death initiated by media starvation (10-13). This suggests a critical action at the level of cell cycle regulation and apoptosis, which we have explored. Taspine has been touted as a principle component of the wound healing actions of Sangre de grado based on its early stimulation of wound repair (14). However, others consider that other chemicals are important, including the polyphenols (10,15).

Sensory Afferent Nerve Mechanisms

Sensory afferent nerves, sometimes called c fibers or primary afferents, serve protective roles, alerting the central nervous system of adverse events in the periphery. They primarily exist in barriers – skin, gut and lungs, where the body's defenses may be breached. The sensitivity of primary afferents can be enhanced by eicosanoids (particularly PGE_2) and nerve activity can be induced by various inflammatory mediators (adenosine, bradykinin, serotonin), glutamate and its own neurotransmitters (CGRP, Substance P) as well as tissue acidification. More recently, we have also demonstrated that protease activated –2 receptors ($PAR\text{-}_2AP$) directly activate primary afferent nerve fibers and lead to hyperalgesia (16). $PAR\text{-}_2AP$ may be activated in vivo by mast cell tryptase (76), which highlights the multi-level interactions between sensory afferent nerves and mast cells (18). Primary afferents innervate mast cells and their neurotransmitters activate mast cells and induce degranulation, as do vanilloids directly (17,18). Tryptase released from mast cell granules then in turn can activate primary afferents, leading to both pain, as well as the sustenance

of neurogenic inflammation. Sensory afferent activation can sustain a number of chronic states of inflammation (19-22). To date this neurogenic component of inflammation has been poorly managed pharmacologically. The major approach has utilized capsaicin, the pungent spice from chili peppers. With repeated exposures to capsaicin the nerve becomes desensitized and lacking in neurotransmitter content (22), but before that can occur the precise mechanisms that are to be attenuated must be activated. Clearly, this is an inadequate approach.

Vanilloids and Sensory afferent Nerves

The term vanilloids chemical structure that interacts with sensory afferent nerves at what is known as the vanilloid receptor. Another common term for this receptor is the capsaicin receptor, as capsaicin the pungent spice of chilli peppers is the prototypical agonist for vanilloid receptors. Vanilloids vary in potency, but the most potent is resiniferatoxin, derived from an African Cactus of the Euphorbaciae family. However, therapeutically, what is needed I not vanilloid receptor agonists but rather receptor antagonists, agents that will reduce pain signaling and neurogenic inflammation. What is needed is the anti-chilli pepper. Sangre de rgado represents just that – the perfect anti-chilli pepper agent, and therefore a new ttherapeutic tool.

It may be only of anecdotal interest, but Sangre de grado and resiniferatoxin are both red saps derived from the genus Euphorbaciae, the genus gave its name to phorbol esters. Sangre de grado is not resiniferatoxin however, as it has no pungency and the origins are old world vs. new world (Africa vs. South America), and structurally one is cactus-like (resiniferatoxin), and the other a fast growing tree. However, tantalizing phylogenic links may exist.

The vanilloid receptor 1 (VR1) has been placed in central importance in regulating the activity of sensory afferent nerves following the development of the VR1 gene deleted mouse model. VR1 KO mice are analgesic to a wide range of painful inflammatory states. However, VR1 KO mice are not immune to all painful stimuli. They display normal responses to noxious heat, thermal pain following nerve injury and to some degree painful heat (23,24). This suggests that VR1 receptor antagonists will provide a broad treatment of inflammatory pain. Most likely sangre de grado will be effective in those pain states associated with tissue injury, and chemical exposure (protons). This limitation is not regarded as a threat to its marketing potential, rather it is important to know that important defense mechanisms still exist, and the potential market share for a VR1 antagonist is still in the multibillion dollar range. Currently, hyperalgesia is managed by NSAIDs (cyclo-oxygenase inhibitors) and opioids that possess pre-synaptic as well as post-synaptic actions (25,26). While effective for many conditions, both of these therapeutic classes possess significant limitations. Opioids are addictive and suffer from tolerance, whereas NSAIDs possess significant side-effects on the gastrointestinal and renal systems.

Novel vanilloids

The search for new structures that interact with the vanilloid receptor has revealed that the classic vanilloid structure present in known vanilloids – capsaicin, resiniferatoxin, capsazepine and zingerone, is not critical for activity. Rather, new structures lacking the recognizable vanillyl motif have been demonstrated to possess significant and encouraging activity (27). Included in

these novel structures are polygodial – a full vanilloid agonist derived from marsh pepper, warburganal – isolated from the bark of warburgia trees which grow in Africa and the Caribbean, isovelleral – another agonist whose terpenoid structure was isolated from fungi, scalaradial - is another unsaturated dialdehyde isolated from sponges, and scutigeral – isolated from edible mushrooms. It is scutigeral that has generated significant interest lately because it lacks pungency (agonistic activity) but its potency is questionable. Thus, there is a growing appreciation that a variety of novel structures can interact with the vanilloid receptor, although few have pure antagonistic activity. These structures have been derived from a variety of natural sources, but we are not aware of any Amazonian botanicals being tested.

Sangre de Grado Actions and Gastric Ulcer Healing

Oral consumption of highly diluted Sangre de grado (1:1000 or 1:10,000) results in an acceleration of gastric ulcer healing in rats (7). The rate of healing is equivalent to the combination of penicillin and streptomycin (28) or novel therapeutic agents like epidermal growth factor (29). Sangre de grado administration was associated with a reduction in the expression of various inflammatory genes in the ulcer bed, including the cytokines IL-1, IL-6, TNFa, and the enzymes COX_2 and iNOS. The gastric ulcer bed becomes rapidly colonized with bacteria, and these bacteria retard healing, as one would expect for any wound. Sangre de grado treatment substantially reduces the bacterial load in the ulcer. While Sangre de grado is inherently antimicrobial the concentrations required for this action far exceed that administered, hence we consider that this reduction in bacterial load was due to an inherent change in the local environment, rendering it unsuitable for bacterial colonization.

Sangre de Grado and Diarrhea

Sangre de grado is an effective agent in managing diarrhea. It is not a paralytic like loperamide. Rather it works through the same mechanism for its analgesic properties. Sensory afferent nerves drive secretory responses in the gut. Sangre de grado was shown to block epithelial secretion in response to capsaicin, the VR1 agonist, but not to Substance P (neurotransmitter) or cholinergic stimuli (7). In addition, acute fluid shifts in response to gut injury induced by acid and undigested protein (a model of bacterially driven intestinal necrosis) was blocked by Sangre de grado at dilutions of 1:1000 (200mg/ml). Interestingly, in addition to preventing the secretory response, Sangre de grado blocked the damage to the intestinal mucosa normally associated with this model. Thus, Sangre de grado is an effective anti-diarrheal that also offers substantial mucosal protective and anti-inflammatory properties.

Sangre de Grado and Analgesia

Hyperalgesia is the heightened sensitivity to painful stimuli. Stimuli that are below threshold for a pain response may become painful when hyperalgesia is induced (PGE_2 is an example of a mediator that acts in this manner). The converse, is analgesia, which is the failure to register pain in response to an agent that would normally induce a pain response. Because of its VR1 antagonistic properties Sangre de grado is an excellent analgesic agent. It is broad acting as the VR1 receptor plays a central processing role pain perception. In other words, inhibition of

VR1 blocks pain perception to a wide range of stimuli. Indeed that is the case with Sangre de grado. It also explains its ethnomedical uses where it is applied topically for broad conditions – insect bites, stings, rashes, plant reaction, cuts and wounds.

Sangre de Grado and Itching

As discussed above Sangre de grado is an effective inhibitor of sensory afferent nerves. These nerves innervate blood vessels, epithelia and mast cells. Activation of mast cells is a critical component of neurogenic inflammation, and for the skin this includes itching. For some skin conditions itching is the most serious symptom. Vanilloid receptors exist on mast cells and drive activation and mast cell derived mediators and enzymes activate sensory afferent nerves. Sangre de grado is a therapeutic agent that interrupts this positive cycle. Clinical tests indicate that Sangre de grado can stop itching responses on average, in less than 2 minutes. Even for difficult conditions like Fire ant bites and poison ivy.

Sangre de grado and Cancer

A small number of studies indicates that cancer cells express a vanilloid receptor and that it is linked to cell death. Of interest is that the degree of cell death evoked by VR1 antagonists far exceeds that of VR1 agonists (30,31). This suggests that the vanilloid receptor responsible is not VR1; vanilloid receptor heterogeneity is well appreciated but full characterization is not available at this time. In vitro, Sangre de grado, results in cancer cell death, at concentrations that are comparable to those required to block VR1 and heal gastric ulcers and acute intestinal injury. While results are preliminary, it is intriguing to consider that vanilloid antagonists may become effective anticancer therapies. In this case it would coincide with a mucosal protective function and analgesia concomitant with cancer regression, through related mechanisms.

Conclusion

Sangre de grado is an excellent example of a medicinal plant that has a profound history of effective use in an indigenous culture, which offers therapeutic opportunities that Western medicine cannot match. Originating from fast growing trees it is efficient to harvest and cultivate and can be applied for a wide range of condition. Sangre de grado also offers an experimental tool to evaluate the role of sensory afferent nerves and vanilloids in health and disease. Sangre de grado and derived formulations will eventually become a critical component of health care delivery for veterinary and clinical conditions including analgesia, topical applications for wounds, skin irritation and inflammation, management of diarrhea and gastrointestinal distress and possibly cancer.

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Traditional Oriental Medicine in Livestock Health

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Abstract

Traditional oriental medicine (TOM) including acupuncture, acupressure, herbology, moxabustion, and Qi Gong is based upon Yin and Yang theory and five-element theory. Eastern medicine, unlike Western medicine has the unification of the subjective and physical world. The fundamental concept of TOM is balancing the body with nature. Therefore, oriental medicine is holistic in its approach to diagnosis and treatment of illnesses.

Herbology (bonchology in Korean or bancaology in Chinese) in TOM has been considered as a principle therapeutic or prophylactic way for humans as well as animals in China, Korea, Japan, India, Tibet along with other Asian countries for thousands of years. Oriental herbs can be divided into two categories, food and medical. Traditional Oriental Veterinary Medicine (TOVM) originated from the Yellow Emperor's Classic of Internal Medicine (475-221BC) in China. Nearly 3,000 herbs are listed in *the Supplement to the Compendium of Meteria Medica* and characterized by the properties, taste and meridian tropism based on TOM. However, there is a limited amount of oriental herbs available for veterinary use.

In general, oriental herb formulas should contain a mixture of several different kinds of herbs in order to increase therapeutic effects, minimize toxicity or side effect, accommodate complex clinical situation, and alter the action of the substances. Oriental herbal treatments based on TOM theory in western countries are still in the experimental stage. Modern researches in pharmacology have been looking for the active ingredients in the individual herb and synthesizing it for pharmaceutical purposes. In western society, the single active ingredient is often extracted for the therapeutic purpose that can induce critical side effects or no effect.

In high intense animal agriculture production systems, antibiotics are commonly used as feed additives to prevent or treat diseases and to improve animal productivity. However, the use of antibiotics in animal agriculture has been documented relating to the emergence of antibiotic resistant bacteria. The prohibition of antibiotic use is now widely accepted by legislatures, consumers, and even food animal industry. In spite of all these facts, food animal producers and pharmaceutical manufacturers still believe that antibiotics are vital to the profitability of animal agriculture. Furthermore, increasing the growth performance is another consideration for the animal producers. To solve our confronted task, we need to identify the specific oriental herbs for antibiotic substitute and for growth performance.

Several researches have studied the antimicrobiol effect of oriental herbs including *Allium sativum, Angelica dahurica, Anguisorba officinalls, Artemisia argyi, Coptis chinensis, Dictamnus dasycarpus, Fraxinus rhynchophylla, Geranium thunbergii, Hydrastis canadensis,*

Phellodenron amurense, Polygonum cuspidatum, Scutellria baicalensis and *Sophora flavesens*. These herbs may be used as a natural antibiotic substitute along with other supportive herbs. The antibacterial effect of Huang qi (Scutellariae Radix) and Lonicera Flos to gram negative bacteria including *Salmonella spp* or *E. coli* and gram positive bacteria *Staphylococcus spp*. and *Streptococcus spp.* are also evaluated. The major flavonoid components, baicalin and baicalein of Huang qi demonstrated the antibacterial effect. Dochaetang extract, herb formula containing Radix paeonia lactiflorae, Radix angelica gigantis, Radix Scutelariae and Rhizoma coptidus has shown the antimicrobial effect against intestinal bacteria. Studies have proved that the root powder from Bupleurum falcatum used as a feed additive enhanced growth performance in poultry.

Oriental herbs for antibiotic or probiotic substitutes should be prescribed and formulated based on the TOM theory. It has been known that herbs having antimicrobiol activity have bitter taste and/or cold in nature. Therefore, prescription with a single herb is not recommended, because long-term use of a herb having bitter taste and/or cold in nature can render some unwanted effect to the body such as weakening the spleen function due to these properties. Furthermore, we recommend not using a single major ingredient solely for these purposes due to the potential possibilities creating critical side effects or no effects. This is why our research team is working to generate several formulas substituting antibiotics and probiotics. The selection, combination and processing procedure of the formulas have been done based on TOM theory. We are trying to provide the evidence based scientific data for our formulas and pre-existed formulas. We believe that this work will contribute to both public health and animal warfare by reducing emerging antibiotic resistant bacteria, diminishing the risk of antibiotic residues in the food and concomitantly, increasing the growth performance.

Alternative Medicine for Animals: FDA Regulations of Dietary Supplements for Animals

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Good morning. My name is Claudia A. Lewis-Eng and I am an associate with the firm Emord & Associates located in Washington, D.C. We represent over three hundred clients who specialize in alternative medicine and dietary supplements, including food and supplements for animals. We represent those clients before the Food and Drug Administration, the Federal Trade Commission and the federal courts.

Today I will provide an overview of FDA regulations for animal food products, including the growing use of dietary supplements with animals.

Nonbiological animal drugs as well as animal foods are regulated by FDA under the Federal Food, Drug and Cosmetic Act. There are two major categories of animal foods and drugs: Those used in nonfood-producing animals (pets) and drugs for therapeutic purposes and those used in food-producing animals

The FDA has the authority to adopt standards of identity, quality and container fill for animal food. FDA can also regulate animal food labeling and animal food adulteration as it does food for humans. However, FDA has not expended its limited resources to develop comprehensive labeling regulations because most states have drafted such regulations.

Instead, FDA has drafted limited labeling regulations requiring that livestock feed and pet food include the name of the food, its ingredients, the name and address of the packer or distributor and the net weight of the product. Indeed, in the area of regulating animals foods and drugs, FDA has formed a unique relationship with the states. Specifically, pet foods, nonmedicated livestock feed and medicated feeds that fall below drug levels that require FDA licensing are regulated by the states through model acts and state regulations. Of course, medicated feeds that require FDA licensure require plant registration, mandatory FDA inspection, and approved FDA medicated feed applications. Most state model acts outline state registration and labeling requirements for the manufacture, distribution and sale of animal foods and drugs.

In regulating animal feed and drugs, most states have adopted the Model Bill drafted by the Association of American Feed Control Officials ("AAFCO"). AFFCO is made up of state regulators and Canadian representatives. AFFCO publishes an annual publication that contains feed and pet food regulations and also individual state feed law requirements. FDA works jointly with AFFCO in regulating animal products.

As many of you are aware, AFFCO has developed separate model regulations for livestock feed and pet food products. Under AFFCO regulations, pet foods must state the nutritional use of the food. For example, the label must state whether the food is for adult animals or for all stages of life. AFFCO requires that manufacturers and/or distributors conduct trials on pet foods using

AFFCO specified protocols to assure that the food is for "adult animals," for "all stages of life," or is "complete and balanced" as claimed on the label.

AAFCO has also developed labeling rules and defined the ingredients that can be used in animal feed, i.e., whether the ingredient is generally recognized as safe for use in animal feed. In fact, FDA recognizes as official the AFFCO –developed feed ingredient names for labeling purposes.

For the most part the AAFCO method of determining and defining ingredients that can be used in animal food has taken the place of FDA's GRAS determination. Under AFFCO's GRAS process an ingredient name and definition is submitted to AFFCO. AFFCO then solicits comments from the industry and state and federal regulators. AFFCO's recommendation about the ingredient is then submitted to and approved by the AFFCO Board of Directors and annual convention of delegates.

Please note however, that a FDA official does participate in AFFCO's GRAS determination and FDA does from time to time identify ingredients that must undergo food additive licensing, which is a rigorous process.

AFFCO has also defined terms such as "lite" or "low calorie" that appear on animal foods. While FDA has defined those terms for human foods, it had not promulgated similar definitions for animal feed and pet foods. To use the terms under AFFCO regulations, the products must meet a standard amount, regardless the manufacturer.

As far as livestock feed is concerned most states require that producers of animal feed register with the state annually. Under federal regulations livestock feed is subject to annual mill inspections to ensure that the animal food is not adulterated or misbranded in violation of the FDCA. If a state is a member of AFFCO, AFFCO members may conduct the inspections in place of an FDA inspection.

While FDA to a large, has extent relied on state regulations for pet foods and animal feed, it has not taken a back seat when it comes to the use of dietary supplementation for animals. Since the passage of the Nutrition Labeling and Education Act of 1990 ("NLEA"), which permitted the use of FDA approved health claims on the labels of human foods, the Center for Veterinary Medicine ("CVM") has attempted to incorporate some the policy of the NLEA to permit meaningful health related information to appear on pet food labels. However, it is important to note that the NLEA did not specifically include pet foods or animal feeds in the law. Accordingly, the NLEA regulations do not apply to animal feeds or pet foods.

In the area of dietary supplements for animals FDA has taken the position that while animals that are on balanced rations do not require extra nutritional supplementation, it does not object to the marketing of dietary supplements for animals provided the following criteria are met:

1. There is a known need for each nutrient ingredient represented to be in the product for each animal in which the product is intended.

2. The label represents the product for use only in supplementation and not as a substitute for daily rations
3. The labeling bears no disease prevention or therapeutic claims including growth promotion
4. The labeling is not false or misleading in any particular
5. The product is neither over-potent nor under-potent nor otherwise formulated so as to pose a hazard to the health of the target animal.

Certified Organic Livestock Production in Connecticut

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The Northeast Organic Farming Association of Connecticut (CT-NOFA) is an independent, non-profit organization dedicated to strengthening the practice of ecologically sound farming, gardening and yard care. It also helps consumers gain increased access to safe, health food. CT-NOFA is one of seven state NOFA chapters in the Northeast. Since 1971, NOFA has been working in support of local organic food production in garden and farms.

One of the main purposes of CT-NOFA is to provide certification of organic farms. The Certification Committee of CT-NOFA exists to provide a credible independent third-party verification of organic food production of Connecticut's farmers and consumers. The basis for organic certification is the method of production and the understanding and commitment of the producer regarding these methods. The method of production will be those practices and substances that are biologically enhancing to the soil, to plant and animal life, to consumers and to the grower.

While CT-NOFA has been in existence since 1982, livestock certification has only been offered since 1995. Since that time there has been a slow but steady increase of certified organic livestock in Connecticut. Certification is offered for organically produced meat and poultry, eggs and dairy. This summer, nine farms received certification for livestock production. Four produce meat for on farm sales, five produce eggs and three produce milk. CT-NOFA also offers a food processing certification for production of cheese for example. Currently one producer is certified to manufacture ricotta cheese.

By the end of this year the federal rule should be published by the USDA will create a national certified organic standard that all certifying agencies will have to follow. The purpose of this rule is to gain uniformity throughout the nation so all organic food sales here and abroad will mean the same thing. After final approval of the rule all certifying agents will apply for accreditation with the USDA to be a certifier under the new standards. There are only minor differences between the CT-NOFA standards and the national standards. It is the hope CT-NOFA that the transition from our standard rule to the USDA rule will be a smooth one.

If you have any questions about the program or are interested in becoming certified contact me at the University of Connecticut Cooperative Extension Systems Organic Farming and Gardening Program

Botanicals for Pigs

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Abstract

The historic use of herbal remedies to treat and prevent infectious disease has been supplanted with the emergence of specific man-made chemotherapeutic and antimicrobial agents. With increasing interest in decreasing the emphasis on these products, studies were undertaken to evaluate the use of four botanicals for swine production. Graded levels of Echinacea, garlic, goldenseal and peppermint were fed to weanling pigs and compared to a standard nursery diet containing 45 ppm Mecadox (carbadox). In general the use of these products did not enhance performance and, in the case of high levels, garlic reduced feed intake and flavored the meat. One reason for the lack of response may have been the high health status of the herd at the Iowa State University Swine Nutrition and Management Farm. Alternatively, the addition of Mecadox was not always beneficial when compared to higher levels of Echinacea.

Keywords: swine, botanical, Echinacea, garlic, goldenseal, peppermint

Introduction

The historic use of herbal remedies to treat and prevent infectious disease has been supplanted with the emergence of specific man-made chemotherapeutic and antimicrobial agents. However, selected herbs are known to possess natural antimicrobial activity and other characteristics that could be useful in value-added (natural) animal protein production. This area of investigation has not received substantive examination because of the relatively low costs, proven effectiveness and availability of synthetic antimicrobial products. The possibility of significant antibiotic resistant bacterial development through the use of human drugs in animals and subsequent transfer of resistance to human pathogens has caused concerns within the medical community. Inclusion of herbs in animal feeds as alternative growth promotion and efficiency stimulating strategies can address some of these concerns while producing a more holistically grown pork product.

The following botanical products have been selected for inclusion in swine feeds based on their pharmacological and agronomic characteristics, which make them applicable to Iowa. Limited information about the use of botanicals in livestock production makes this evaluation timely.

Echinacea (purple coneflower)

Echinacea species are perennial herbs capable of growth throughout the Midwestern USA. There are nine species, but *E. augustifolia, E. purpurea* and *E. pallida* are most commonly considered for medicinal purposes (Taylor, 1968). The whole plant, including aerial portions and taproots, has been utilized. Additionally, pressed juice from the aerial portion of *E. purpurea* and aqueous and alcohol extracts of the roots have viral inhibition characteristics in cell culture

(Wacker and Hilbig, 1978). The German government has approved oral use of Echinacea for respiratory and urinary tract infections and topically for improving wound healing. Liquid preparations have been shown to have immune-stimulating activity and enhance several white blood cell types as well as phagocytes (cells that can destroy bacteria and protozoa (Burton Goldberg, 1999)).

Garlic (Allium sativum)

Garlic, a member of the lily family, is a perennial plant cultivated worldwide. Garlic bulbs, either fresh or dehydrated, are used for medicinal purposes. The bulbs contain volatile oils composed of allicin, diallyl disulfide, and diallyl trisulfide, which are considered the reservoirs for most pharmacological properties attributable to garlic. Garlic demonstrates a broad-spectrum antimicrobial activity against many bacteria, viruses, parasites and fungi (Hughes and Lawson, 1991). Garlic has also shown an ability to aid certain immune functions, particularly increasing natural killer cells' activity (Foster, 1991)

Goldenseal (*Hydrastis canadensis*)

Goldenseal, native to eastern North America, is a perennial herb. The most pharmacologically active isoquinolone alkaloid, berberine, is concentrated in the rhizome and roots. Berberine has been demonstrated to possess antimicrobial, immuno-stimulatory, anticonvulsant, sedative, hypotensive, choleretic and carminative activity. This antimicrobial activity has been demonstrated against a wide range of bacteria, protozoa and fungi (Duke, 1985). Berberine and berberine-containing plants are generally considered non-toxic. The LD50 for berberine in rats was reported as greater than 1000 milligrams per kilogram body weight (Hladon, 1975).

Peppermint (*Mentha piperita*)

Peppermint grows under a wide range of conditions. The most popular varieties are black peppermint (*Mentha piperita* var. *vulgaris*) and white peppermint (*Mentha piperita* var. *officinalics*). The major medicinal components of peppermint are the volatile oils found predominantly in the aerial portions of the plant. The principal components of these oils are terpenoids, menthol, methone and menthyl acetate. Other components that may have pharmaceutical properties include polyplenols, flavonoids and betaine.

Menthol possesses carminative, antispasmodic and cholerectic properties. Peppermint and other members of the mint family have demonstrated significant antiviral capability including treatment of the common cold (Kerman and Kucera, 1967). Peppermint also inhibits antimicrobial activity against *Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candida albicans* (Sanyal and Vamra, 1969). The LD50 of menthol in rats is 3,280 mg/kg and a fatal dose for humans was reported as 1 g/kg. Hypersensitivity reactions (skin rashes) have also been reported (Briggs, 1993).

Experimental Design

These experiments were conducted at the Iowa State University Swine Nutrition and Management Center in temperature-regulated nursery rooms. Pigs were weaned at an average of 18 days (14 to 21) and 6.25 kg. They were allotted at random to pens by litter and initial weight immediately following weaning. There were 20 or 24 pens of five pigs each, providing four to six replications of the dietary treatments. Each pen received 16 kg of the prestarter treatment per pig and then was switched to the starter treatment diet for the remainder of the five-week study (Table 1). The positive control diet contained 45 ppm of Mecadox (carbadox). Botanical treatments consisted of the same diet without Mecadox and increasing levels of botanicals replaced corn, with the 0% level considered the negative control. Pigs were grown in 1.2 x 1.2 meter raised-deck pens and the average room temperature was 24 ± 2°C. Heat mats supplied supplemental heat. Pigs were weighed and feed disappearance measured weekly for five weeks. In the first year (1997) of studies the project was completed at the end of the nursery phase. In 1999-2000, when the Echinacea, garlic, and peppermint studies were repeated, upon completion of the nursery phase pigs were fed the standard farm grower (Tylan, 36 ppm) and finisher (BMD, 27 ppm) diets. Medications were included because of an ileitis infection. Post-nursery weights were recorded every four weeks to evaluate long term effects of the nursery treatments. Average daily gain (ADG), average daily feed (ADF), and feed efficiency (F/G) were analyzed using the GLM procedure of SAS with the pen as the experimental unit. Least square means are presented in the tables.

Where appropriate, one pig at the end of the nursery phase from each botanical treatment was taken to the ISU Meat Laboratory, slaughtered, and various muscles evaluated for sensory and quality characteristics. Pigs fed Mecadox were not slaughtered because of a 42 day withdrawal requirement.

Between the first set of trials (1997-1998) and the second set (1999-2000) the farm was depopulated and repopulated. The herd currently is at a high health status, being Porcine Respiratory and Reproductive Syndrome (PRRS) free. This high status may have reduced the need for medications in the nursery.

Table 1. Example diets

Ingredient	Prestarter	Starter
Corn, yellow	36.43	51.57
Whey, dried	25.00	10.00
Appetein	5.00	0.00
Soybean meal, dehulled	29.20	33.50
Dicalcium phosphate	1.65	2.19
Limestone	0.90	0.78
Salt	0.00	0.25
Lysine, synthetic	0.20	0.20
Methionine, DL	0.10	0.10
Vitamins, Trace minerals	0.52	0.41

Animal fat, stabilized	1.00	1.00
Mecadox 2.5/Botanical	--	--
Total	100.00	100.00

Calculated analysis of example diets (%):

Nutrient	Prestarter	Starter
Lysine	1.46	1.28
Methionine + cystine	0.88	0.66
Calcium	0.79	0.79
Phosphorus, total	0.72	0.70
Phosphorus, available	0.48	0.41

Summary and Implications

Echinacea I

At the tested inclusion levels (0, 0.1, 0.5 and 2.0%) no statistical advantage existed when compared with the diet containing 45 ppm Mecadox or with a "negative" control containing no antimicrobial or botanical inclusions. Echinacea-treated pigs exhibited a slight, but not objectionable, off-flavor when compared to pigs fed non-inclusion levels. The study noted that in weeks 0-3 and 0-4 the higher levels of Echinacea (0.5 and 2.0%) were significantly more efficient ($P<0.05$) but daily gain and feed intake were not statistically different. Total performance for the entire experiment, Weeks 0-5, was not statistically different. These data suggest higher levels of Echinacea enhanced feed efficiency compared to the 0% Echinacea during the first two weeks and were greater than the Mecadox diet during the Weeks 0-3 and 0-4. Overall, performance was similar, suggesting minimal subclinical stress during this experiment. Higher levels of Echinacea may be required to enhance growth rate and feed efficiency.

Echinacea II

This trial evaluated lower levels than in Echinacea I to reduce feed costs and potentially maintain some of the feed efficiencies observed. Mecadox or Echinacea (0, 0.10, 0.25 and 0.50%) replaced corn. One pig was removed during the nursery phase and one during the finishing phase. In Week 1 there were no statistical differences, indicating similar performance between the treatments. Subsequent performance indicated no advantage for feeding Echinacea with the exception of Weeks 0-2 and 0-3 when a significant quadratic observation was observed for the Echinacea levels for feed/gain. The Mecadox diet had significantly better performance than the treatment levels of Echinacea in Weeks 0-2, 0-3, 0-4 and 0-5. Growth rate during the post-nursery phase was not affected by nursery treatments. These lower levels of Echinacea failed to enhance performance.

Echinacea III

This trial was initiated to explore higher additions of Echinacea. Mecadox (45 ppm) or Echinacea (0, 1.50, and 3.00%) replaced corn. No pigs were removed during the nursery phase.

During the grow-finish phase one poor-doer was removed from the Mecadox treatment and a ruptured pig was removed from the 3% Echinacea treatment. There were few treatment differences. Mecadox generally increased daily gain in Weeks 0-3 and 0-5 ($P<.01$). Echinacea additions depressed feed/gain in Weeks 0-2 and 0-3. However, 3% Echinacea enhanced overall gain in the Week 0-5 nursery period when compared to 0 and 1.5% levels and supported gains equal to the Mecadox diet. No significant gain responses were observed post-nursery although the highest level of Echinacea fed during the nursery supported gains equal to the Mecadox pigs. Neither Mecadox nor Echinacea were fed after the nursery period.

Garlic I

At the tested garlic inclusions (0, 0.5, 2.5 and 5%), increasing levels of garlic generally depressed feed intake and average daily gain in nursery pigs and depressed performance compared to the Mecadox diet. Muscle samples from all slaughtered pigs had "very objectionable" or "extremely objectionable" off-flavors. This suggests that the garlic odor was sufficiently strong in the room that it also flavored muscle samples of pigs not fed garlic. A visitor's first observation was that the room and adjacent hallway had a very strong, objectionable odor of garlic combined with hog manure throughout the nursery phase.

The overall summary, Week 0-5, indicated the Mecadox diet significantly improved daily gain compared to the garlic treatments ($P<.01$ to $P<.05$); generally the higher the level of garlic, the poorer the daily gain. Mecadox ADF was significantly greater than the 5% level of garlic ($P<.05$). Overall feed efficiency favored the 0% garlic diet, but was statistically different only from the 2.5% garlic treatment.

The 5.0% level of garlic significantly reduced feed intake in Weeks 0-2, 0-3 and 0-5 when compared to Mecadox ($P<.01$ and $P<.05$). Additionally, in Weeks 0-3 as the level of garlic increased, feed intake decreased.

Garlic II

The second garlic trial fed inclusion levels of 0.00, 0.10, 0.25 and 0.50% garlic, levels that hopefully would be low enough not to depress performance or alter meat flavors. Pigs fed diets without Mecadox demonstrated significantly poorer performance. Based upon this and the 1997 study, pigs fed diets with Mecadox performed better. The addition of garlic did not enhance pig performance. Because of the garlic flavoring of the pork in the first garlic study (Table 6) muscle samples were tested at the end of the nursery period and again two weeks later. At the end of the nursery phase, a slight garlic flavor was detected in muscle but after two weeks on a garlic-free diet no garlic flavor was detected.

Goldenseal I

This study evaluated four levels of goldenseal (0.0 to 1.0%) to a diet containing Mecadox. Although not performing to the level of the Mecadox-fed pigs, those fed 0.25% and 1.00% goldenseal diets performed numerically better than the 0.00% and 0.05% goldenseal diets.

Mecadox-fed pigs generally performed statistically better than the other treatments. Increasing levels of goldenseal did not influence the muscle characteristics evaluated.

Some F/Gs appear unreasonable because of an occasional pen with very poor gains with normal or high feed intakes. In Week 1, the Mecadox diet produced daily gains ($P<.05$) greater than the 0.00% goldenseal diet and feed intake greater than the 0.05% goldenseal. This suggests additions of goldenseal produced performance comparable to the Mecadox pigs during the first week. During weeks 0-2 the Mecadox diet ADG was significantly greater than the 0.00% diet ($P<.05$) and tended to be greater than the three higher levels of goldenseal. Mecadox F/G was improved over the 0.00% and 0.05% goldenseal but not statistically different from the higher levels.

Weeks 0-3 had significantly greater ADG and ADF for the Mecadox pigs over the other treatments. The ADF of the two highest levels of goldenseal tended to be greater than the 0.00% negative control. Mecadox-fed pigs F/G was not statistically different from the two highest levels of goldenseal and significantly greater than the 0.00 and 0.05% diets, with the two highest levels also having improved efficiency compared to the 0.05% diet. During Weeks 0-4 the Mecadox diet ADG was significantly higher than the 0.00% and 0.05% goldenseal diets ($P<.05$). Overall feed efficiency was lowest for the Mecadox diet when compared to the 0.00% and 0.05% treatments but not statistically different from the two highest level. The two highest levels tended to be more efficient than the 0.00% and 0.05% goldenseal diets.

Peppermint I

Nursery pigs fed inclusion levels of peppermint (0, 0.5, 2.5 and 5.0%) failed to respond to added levels. Pigs on all treatments (including the Mecadox and 0% peppermint) performed similarly over the entire experimental period. The 5% pigs in Week 1 required significantly more feed per pound of gain than the Mecadox pigs ($P<.05$), probably because of the bulkiness of that diet. During Weeks 0-2 the 0% pigs required significantly more feed than both Mecadox and 2.5% peppermint pigs ($P<.05$). Generally the Mecadox pigs and the added peppermint pigs performed similarly during this period. No statistical differences were observed after the first two weeks ($P>.05$).

Peppermint II

This experiment evaluated Mecadox and 0, 0.5 and 1.0% peppermint levels under a similar feeding regimen plus a 12-week post-nursery evaluation to observe any carry-over effects. Peppermint failed to elicit a positive nursery response and those pigs performed more poorly statistically when compared to the Mecadox-fed pigs. Pigs fed Mecadox maintained their advantage when cumulative performance was evaluated for the additional 12 weeks, but performance within each weighing period was not statistically different after the nursery phase. Under the conditions of this experiment peppermint, as in Peppermint I, was not an efficacious addition to swine nursery diets.

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Mastitis Control: Lessons from the Vermont Nosode Study

Evaluation of Homeopathic Nosodes for Mastitis and Calf Scours, and Documentation of Homeopathic Practices in Dairy Production.

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Introduction

Mastitis continues to be considered the most costly disease of dairy cows (Fetrow et al. 2000). Mastitis also has numerous detrimental effects on milk quality and composition. Unfortunately, the use of antibiotics has not proven totally effective in curing all types of existing udder infections during lactation, and the use of antibiotics increases the risk of residues in milk and dairy products (Hady et al. 1993). Alternative treatments and preventative measures should be evaluated as methods to reduce the incidence of new mastitis cases and to eliminate existing cases.

Neonatal diarrhea is a major cause of dairy calf morbidity and mortality, and can result in significant financial loss on dairy farms. Eliminating neonatal diarrhea can be labor intensive and frustrating. Neonatal diarrhea caused by *Escherichia coli* is of particular concern on many dairy farms.

Homeopathic nosodes have been recommended as an alternative to conventional therapies for the prevention and treatment of bovine mastitis and *E. coli* calf scours. It has been suggested that homeopathic nosodes function in a manner similar to conventional vaccines, in that they may act to increase the natural resistance mechanisms of the cow, and thus prevent establishment of new infections and enhance the cure rate of existing infections (Day, 1986; Day, 1995; Macleod, 1991; Stopes and Woodward, 1990).

Methods

A research project evaluating the effectiveness of nosodes for mastitis and calf scours was initiated in September 1997 with the enrollment of 11 dairy farms, including over 1000 lactating cows and 300 calves. Table 1 contains descriptive information on the original 11 farms participating in this study. The research was conducted by the Northeast Organic Farming Association of Vermont with the collaboration of the University of Vermont Quality Milk Research Laboratory, and was funded under a grant awarded through the USDA Northeast Sustainable Agriculture Research and Education initiative (SARE). The first three months of the project were spent meeting with participating farmers to educate them about the research process. Time was devoted to training of farmers on proper milk sampling and nosode treatment procedures. This was critical to assure compliance by the participating farmers. Ten of the original 11 farms completed the 18 month study period, with farm 3 removed from the study due to evidence of improper treatment administration and poor milk sampling practices.

Nosode preparation and administration: The E. coli nosode used was a commercially available product from Washington Homeopathics. Farmers that chose to participate in the E. coli study gave newborn calves one of two treatments, the nosode or placebo control which were randomly labeled on each farm as treatment "A"or "B" so that both farmers and researchers were blinded to the treatments given. Treatments were given to all new-borne calves once daily for the first 3 days of life. The calves were assigned alternately to group A or B to assure equal numbers in the treatment and control groups, and in an attempt to randomize treatments. Producers recorded all health problems of the treated calves during the first 3 weeks of the calves' life.

A mastitis nosode was prepared commercially from common mastitis pathogens isolated from cows within the cooperator herds. Lactating cows in participating herds were stratified by lactation number, days in milk, and composite milk somatic cell count (SCC), prior to being randomly assigned to two treatment groups. Heifers entering the study prior to expected calving date were alternately assigned to a treatment group. Each treatment group was given either the mastitis nosode or the placebo as an aerosol applied to the vaginal mucosa at recommended time intervals throughout the trial. As a double blind experimental design, only the consulting veterinarian who coordinated nosode preparation knew which treatment group received the placebo or the nosode for each farm, and the key to the treatments was maintained in a sealed envelop until the completion of the trial.

The mastitis nosode was prepared from quarter milk samples obtained from cows with clinical mastitis from the participating farms. The milk samples from these individual cases were cultured to identify the pathogen causing mastitis. Thus clinical milk samples were obtained from cows where a single mastitis pathogen was identified to be causing mastitis. The nosode was prepared at a 30C potency from clinically abnormal milk samples where the following mastitis pathogens had been isolated: *Staphylococcus aureus*, *Staphylococcus chromongenes*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, *Escherichia coli*, and *Klebsiella spp.* Milk samples, obtained from two farms per pathogen, were randomly selected to be used for the final mastitis nosode. The following farms contributed clinically abnormal milk samples for the mastitis nosode (samples taken November 1997): *Staphylococcus aureus*, farm 2 and 6; *Staphylococcus chromogenes*, farm 4 and 9; *Streptococcus uberis*, farm 2 and 9; *Streptococcus dysgalactiae*, farm 1 and 4; *Escherichia coli*, farm 3 and 8; *Klebsiella spp.*, farm 1 and 8 (Table 1).

Treatment procedures: In all cooperator herds, the mastitis nosode and placebo were diluted in a solution of 50% alcohol and administered as an aersol spray applied to the vaginal mucosa of dry cows, lactating cows, and bred heifers. Treatments were administered initially for 5 consecutive days, and then once every two months for the remainder of the study on all animals, plus at calving and at dry off for all lactating animals.

Farmers were instructed to manage all animals that developed clinical disease (including mastitis or calf scours) according to established practices for each farm. Farmers were asked to record all disease events, treatments and the outcomes, although no formal criteria and protocols for recording clinical disease events were established in this study.

Measures of efficacy: Effect of treatment on mastitis rates was evaluated by bacteriological culture of milk samples from all cows collected at calving, 30 days post-partum, dry off, the onset of clinical mastitis prior to any treatment, and 30 days following the onset of clinical mastitis. Duplicate individual quarter milk samples were collected aseptically by cooperating farmers. Samples were either refrigerated and delivered to the laboratory within 24 hours, or were stored frozen and delivered to the laboratory with 2 to 3 weeks after collection. Milk samples (0.01 ml) were streak-plated on quadrants of tryptose-blood agar containing 5% washed bovine red cells and 0.1% esculin. Plates were incubated at 37°C for 48 hours and presumptive diagnosis of isolates made. Species identification was by methods recommended by the National Mastitis Council. A quarter was diagnosed as infected by one of the following criteria: 1) both milk samples contained 500 cfu/ml, or more, of the same bacterial isolate; or 2) a clinical sample contained at least 100 cfu/ml of an isolate. Somatic cell counts of all individuals quarter milk samples were determined using a Fossomatic 90. In addition, all herds enrolled in the study were either on monthly DHIA testing for individual cow milk production and composite SCC, or obtained monthly milk production and SCC data by an alternative means.

Differences between treatment groups in prevalence of all IMI, prevalence of new IMI, rates of clinical mastitis, and spontaneous cure rates of IMI were examined. Spontaneous cure was defined as negative for the same species (or a closely related species, in the case of coagulase negative staphylococci) on two subsequent samples. Also, differences in SCC of infected quarters were compared between treatment groups. A modified Student t test was used to compare differences in proportions for prevalence of IMI and spontaneous cure between treatment groups. Control and treatment groups were compared for differences in distribution of cows by lactation number and DIM throughout the study, and for SCC prior to initiation of the treatments. Treatment effects were tested within parities (lactation number) one and two or greater. Differences in SCC of infected quarters between treatment group were examined by analysis of variance. Differences between treatment groups in average monthly milk production and composite SCC of individual cows was examined by analysis of variance. Season and month of study were considered as dependent variables affecting milk production and SCC.

Clinical mastitis cases were identified by each farmer. Clinical mastitis was defined as the presence of abnormal milk secretions, abnormal swelling of the gland, or both. Clinical mastitis may or may not be accompanied by systemic signs of illness such as loss of appetite or fever. Farmers collected milk samples from all quarters of cows with clinical mastitis, prior to initiation of any mastitis treatments. Farmers or veterinarians treated clinical cases as per commonly practiced on each farm, and all treatments were recorded. The overall and the pathogen specific incidence rates of clinical mastitis were compared between treatment groups on individual farms and on all farms. The incidence rate of clinical mastitis was expressed as number of quarter cases per 1000 cow-days at risk. Only lactating cow days were considered in the calculation of total number of cow-days at risk for treated and control cows on each farm. The number of lactating days at risk for each cow was determined using individual cow DHIA records. Differences in rates of clinical mastitis were tested by Fisher's exact probability test.

Bulk tank milk samples were collected weekly and frozen for subsequent analysis. Bulk tank milk samples were analyzed by bacteriological culture and somatic cell count. Changes in bulk tank somatic cell count and bacteriology will be examined for the 6 months prior to, for the 18 months during, and for the 6 months following the study.

Results

An abundance of anecdotal information and case histories strongly suggest that homeopathic remedies effectively prevent mastitis. To the best of our knowledge, this project involved the largest placebo controlled, double blind clinical field trial of nosode efficacy for the prevention of mastitis among dairy cattle. This study was conducted on 10 different farms that use conventional and organic production practices and ranged in size from 20 to 250 lactating cows. Collaborating farms used a range of management practices, including: intensive seasonal rotational grazing systems feeding strictly grass forages and a small amount of grain for 6 months of the year, and year round confinement systems feeding a total mixed ration to maximize year-round milk production.

One important outcome of this project was the documentation of the use of homeopathic remedies on farms and the development of a resource for more information on how different remedies may be used successfully.

***E. coli* nosode efficacy:**

A total of 287 calves were enrolled in this portion of the project. Rate of scours in the nosode treated group did not differ from the control group for either calves with scours at all ages, or calves with scours between days 0 and 7 postpartum.

Mastitis nosode efficacy:

Rates of new intramammary infections (IMI) among primiparous and multiparous cows treated with the homeopathic nosode did not differ from that of cows in the control group. These results are consistent with what might be expected if mastitis nosodes function in a manner analogous to that of an autogenous vaccine. Rates of new infections would most likely be effected by changes in management practices that effect either the prevalence of pathogens in the environment or the susceptibility of cows in the herd. A vaccine administered to a host is likely to have limited effect on environmental prevalence of many mastitis pathogens. These results are consistent with those observed for the one proven efficacious mastitis vaccine presently used by the dairy industry. The *E. coli* J-5 vaccine has been shown in field trials to have no effect on the rate of new IMI, but to effectively decrease the severity and duration of *E.coli* mastitis (Hogan et al., 1992). If mastitis nosodes function in a manner analogous to a vaccine, then differences in spontaneous cure rates and rates of clinical mastitis might be expected. Data analysis continues to identify potential differences in mastitis cure rates and rates of clinical mastitis, as well as potential differences in somatic cell counts between nosode treated cows and cows receiving the placebo.

Discussion

We present here some preliminary results of placebo controlled double blind studies conducted in Vermont to assess the efficacy of mastitis and E. coli nosodes used in dairy cattle. These studies should be considered a starting point for the critical evaluation of alternative therapies used in food animal medicine.

In order to further stimulate discussion we present some comments on the challenges with the study design, and some issues that have been brought to our attention concerning the study of homeopathy. We conclude with a review of the considerations for the design of field trials to study homeopathy.

Challenges with the design of the study

In general, the herds involved in this study were run by good managers. The high quality of these herds may have influenced the results of the study, because they entered the study with relatively low somatic cell counts, and low rates of clinical mastitis. Thus the opportunity to observe dramatic differences in cure rates may have been limited. However, this must be weighed against the possibility of poor compliance of managers who demonstrate a lower standard of milk quality and udder health. Barkema et al. (1999) studied management style and the association with bulk tank milk somatic cell count, and found that there was a strong relationship between a "quick and dirty" management style and a high bulk milk SCC, and that the farmers with a high bulk tank SCC implemented mastitis prevention measures less often and for shorter periods.

Just by being in a study, the participants may become more aware of their mastitis prevention practices, and improvements in overall udder health and milk quality might be expected.

Cooperator herds were not always good at taking milk samples on time. Sometimes a few days post fresh instead of on the day she freshened (for example). This should not be a significant problem, as for majority of samples were taken within an acceptable range of days.

Some farmers were more observant and treated cows for situations that may have gone overlooked on other farms. For example, a number of organic herds recorded clinical mastitis cases in the early dry period, which raises the question of whether this was a measure of better observation of dry cows or a result of lack of dry cow therapy use on organic farms? Regardless, the number of 'clinical' cases reported for a herd depended on farmer observation.

Other Issues:

1) Nosode Administration

A lot of preliminary discussion on nosode administration took place with the help of two experienced large animal homeopathic vets, Dr. Steve Woodard and Dr. Edgar Sheaffer. It is important for the nosode to come in contact with the mucous membranes and our choices were the

mouth, nose, eye or vulva. We decided that the best way to treat the animals, with the smallest risk of the animals treating each other, was by administration in the vulva of individual cattle. The farms involved had various management styles, including: 100% confinement in freestalls, tie barn housing with access to pasture, and freestall housing with access to pasture. We knew that we could not ask the farmers to divide their herds into two groups for administration in separate water sources. We wanted to find a way to conduct an experiment where the cooperating herds could continue managing their animals the way they normally do. Further, by not housing treatment groups separately, an additional source of "pen" or "group" bias was avoided.

One of the participating farmers pointed out, since we really know so little about how homeopathy does work, is it possible that the cows that are getting the placebo are actually getting 'treated' by the other cows just by rubbing noses, sharing the same space, grazing the same ground?" There is so little that we know about how homeopathy works. Is it possible to study its effects in a conventional, reductionistic design when it may work in a more holistic, energetic way? How do you measure such effects?

2) Why booster the animals every two months, at calving and at dry off?

Steve Woodard found that when using a mastitis nosode on other farms, it is necessary for the nosode to be given to all the animals a minimum of every 5 months. We decided that, for safety, we would booster them every 2 months to make sure the there is no reduction in the effects of the treatment. We also felt that, since the animal is being handled at calving and dry off, and since there tends to be a certain amount of stress at these times, it would be good to give the animals a booster at these times as well.

The mastitis nosode is a 30 C potency in a 50% alcohol solution. The alcohol solution gives the nosode a longer shelf life making it affective for at least 5 months provided it is stored in a cool dry place

3) Why look at bacteriologic outcomes, when homeopathy may be acting in a more holistic way?

The use of homeopathic remedies is being promoted for the treatment and prevention of mastitis. Given this objective, it seems appropriate to test a hypothesis that homeopathic nosodes are significantly better then no treatment for the prevention of mastitis. In order to test this hypothesis it seems appropriate to use a discrete outcome such as differences in prevalence and incidence of bacteriologic infections, or bacteriologic cure rates. Homeopathy is being promoted as a treatment alternative for mastitis, so discrete measures of mastitis risk and occurrence are indicated – if homeopathy were being promoted only as a method to enhance the vitality of the whole farm system, then outcome measures of a more holistic nature would be more appropriate.

Response to the nosode

The response to the nosode is supposed to be very fast. A first response can be discharge; a lot of junk (aggravation) is part of a homeopathic treatment. This is just the animals response of

cleaning itself out.

Discussion of design and critical features of field trials

Practitioners and producers require information about the effectiveness and safety of treatments and preventatives such as pharmaceuticals, vaccines, and alternative therapies. Information may come from numerous sources including anecdotal clinical experience (personal and collective), laboratory studies, and clinical field trials. Information obtained from well-designed clinical field trials may provide some of the strongest evidence of the efficacy of specific therapeutic options. But such information is often lacking for both conventional and alternative therapies in veterinary medicine. Elbers and Schukken (1995) described the critical features of veterinary field trials in their review of veterinary field trials of drug and vaccine efficacy published in the Veterinary Record from 1988 to 1992. This review provides a list of criteria for the evaluation of field trials (table 4). In this review it was noted that a considerable number of papers lacked details of the study design and a formal analysis of the data. Of particular concern were the number of papers that: 1.) used small numbers of animals in treatment groups (46% with $\leq$ 10 animals per group); 2.) did not state that treatment allocation was random (50%); 3.) did not use or state whether treatments were blinded (94%); or 4.) did not make a formal statistical analysis of results (25%). Similar reviews of study design quality have been completed for published clinical trials of homeopathic therapies used in human medicine (Kleijnen, et al., 1991, and Linde, et al. 1997). The same types of concerns were raised in these reviews, with issues of study population size, appropriate control groups, randomization, double blinding, and adequate statistical analysis being of particular concern (table 4). Kleijnen et al.(1991) found a surprisingly small number of published human clinical trials on homeopathy that are of high methodological quality. Despite these results, these authors stated they were surprised by the amount of positive evidence in favor of homeopathy, even among the trials with higher methodological quality. Based on the amount of positive results the authors stated they "would be ready to accept that homeopathy can be efficacious, if only the mechanisms of action were more plausible." Similar, positive trends were observed by Linde et al. (1997) in their meta-analysis of the human clinical trial literature. In summary, both reviews of the human literature suggest that the evidence from clinical trials of homeopathy "is positive, but not sufficient to draw definitive conclusions because most trials are of low methodological quality" (Kleijnen et al. 1991). In addition to the issue of methodological quality of clinical trials, two other issues are raised by these reports with regard to the study of homeopathy. First, is the possible effect of publication bias on a review of the literature, and second is the question of conducting research on a treatment modality where the mechanism of action is not completely understood.

With regard to publication bias, the extent to which this bias effected the conclusions of homeopathy efficacy in the reports by Linde et al. and Kleijnen et al. is unknown. The journal of publication and the bias of scientific reviewers for a particular journal may affect the publication of a clinical trial on alternative therapies. This was recently illustrated in a publication by Resch et al. (2000). These authors submitted two versions of an invented report describing a randomized, placebo controlled, trial of appetite suppressants to reviewers of scientific medical journals. Resch et al. compared the review of conventional "questionable" appetite suppressant

(hydroxycitrate) with an unorthodox controversial drug (homeopathic sulphur), where the only difference in the two manuscripts was the name of the therapeutic. They identified a significant bias among reviewers in favor of the conventional version of the manuscript for the invented "research trial." They concluded that: "studies incongruent with *a priori* beliefs tend to be rated by outside reviewers as incompetently conducted." But the authors noted that while the bias observed "may put authors of unconventional papers at a disadvantage," they suggested the disadvantage was not large enough to preclude publication in peer-reviewed conventional journals." They concluded that reviewer bias "does not explain the scarcity of methodologically sound papers on unconventional treatments in peer reviewed journals."

It has been suggested that it may be inappropriate to conduct research on treatment modalities were the mechanism of action is unknown or does not conform to current theories. Yet defenders or enthusiasts of alternative treatments typically suggest that there are many conventional therapies in common clinical use where the mechanism of action is incompletely understood. This may be true, and examples of efficacious conventional therapies where the mechanism of action are poorly defined may be presented, however, the understanding of these therapies is typically supported by accepted pharmacological mechanisms. Perhaps, a more relevant question may be that proposed by Kleijnen et al. (1991), "Are results of randomized double blind trials less convincing because there is no plausible mechanism of action?" The answer to this question may be no, as Wynn (1998) seemed to suggest, since the theories on the homeopathy's mechanism of action are speculative. And while the reports of electromagnetic differences or unique energetic frequencies of homeopathic preparations might provide some vague clues to possible mechanisms of action, these reports do little to suggest a physiological cause and effect relationship between the treatment and the outcome. Therefore, it is likely appropriate that researchers concentrate on trying to detect a clinical effect of treatment, especially given the increasing interest in, and the amount of emotional debate engendered by, homeopathy.

It is clear from these reviews that improvements in trial design and data analysis are necessary in clinical field trials of both conventional and alternative treatment modalities in veterinary and human medicine. There is no reason to believe the influence of publication bias, data massage, bad methodology, etc. is less in conventional medicine then in alternative medicine research. However, the unique nature of homeopathy suggests that rigorous attention to detail in study design and data analysis may be required for the publication of clinical research trials on homeopathy. While Wynn (1998) has provided a review of studies on homeopathy in veterinary medicine, no assessment of the methodological quality of veterinary homeopathy research has been made. In the future, it appears that a critical review of clinical trials of homeopathy in food animal species is warranted.

It also seems clear from these reviews, that it is possible to perform trials on the efficacy of homeopathy in a way that is acceptable to both classical (i.e. skeptical) physicians, and enthusiastic homeopaths (Kleijnen et al. 1991). Schukken and Deluyker (1995) provided a summary of the design and analysis of field trials for the evaluation of the efficacy of products for treatment of bovine mastitis. The recommendations made in that paper may also be applied to the design and analysis of products recommended for mastitis prevention, including alternative treatments such as homeopathy nosodes. In addition, the features (or criteria) for design of field

trials for the evaluation of mastitis therapies are similar to those suggested for the evaluation of human homeopathic therapeutics (table 1), so it should be possible to design clinical field trials of high methodological quality for the study of alternative therapies for mastitis prevention and treatment. Key among these design features is defining the trial objectives and the hypothesis being tested, reducing bias and confounding influences, assuring appropriate randomization and blocking, selecting appropriate experimental units, reference populations, and study populations. Defining appropriate treatment regimens (including blinding), and relevant response measures or outcomes, is also a critical component of study design. Finally, appropriate statistical analysis and reporting of results must be planned for prior to initiation of the study. One complication to be considered in the study of homeopathy is the consistent application of an individual treatment regimen for a clinical case, and different potencies of various remedies may need to be compared, as "virtually no evidence exists about the correct choice of remedy or potency" (Kleijnen, 1991). A related difficulty is the apparent disagreement among homeopathic practitioners concerning the efficacy of the various types of homeopathic preparations and practices, including disagreements on the efficacy of prophylactic use of nosodes, or on the use of combination preparations to treat an animal with a clinical disease such as mastitis based only on the presenting sign of mastitis, and not a larger spectrum of signs and symptoms.

Using the criteria in table 1 it should be possible to complete a review of literature on the use of homeopathy to prevent and treat mastitis in dairy cattle. Such a study is currently being conducted, and approximately 50 publications on the use of homeopathy for treatment of mastitis have been identified. Similar to the findings reported in the human literature, few of these publications appear to be of high methodological quality. Therefore the criteria described by Schukken and Deluyker for the design of mastitis therapy trials must also be applied to future studies. If skeptical practitioners are asked to accept the results of clinical field trials of homeopathy in food animal medicine, then additional evidence must consist of well performed controlled trials with large numbers of participants under rigorous double blind conditions.

Table 1: Criteria and features for assessing the quality of clinical field trials

Feature	Reference[1]			
	Schukken & Deluyker (1995)	Elbers & Schukken (1995)	Kleijnen, et al. (1991)	Linde, et al. (1997)
Characterize the patient population or case adequately (describe symptoms, duration, severity)	Yes	No	Yes	Yes
Number of treatment groups and the inclusion of a control group	Yes	Yes	Yes	Yes
Numbers of animals in each treatment group relative to the number in the control group	Yes	Yes	Yes	Yes
Random allocation of animals to the treatment and control groups (confounders eliminated)	Yes	Yes	Yes	Yes
Intervention (treatment) well described (repeatability of trial)	Yes	No	Yes	Yes
Single or double blinding	Yes	Yes	Yes	Yes
Outcome well defined (measurable)	Yes	No	Yes	Yes
Descriptions of statistical analysis applied	Yes	Yes	Yes	Yes
Calculation of the type II error and statistical power	Yes	Yes	Yes	No
Potential problems associated with clustering of patients due to housing or grouping for management	Yes	Yes	No/NA	No/NA

1. Yes, if authors included the feature or criteria in their review; No, if the feature or criteria was not mentioned in the reference. NA= may not be directly applicable in human trials, however clustering within treatment groups may be possible

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Alternative Methods of Disease Prevention in Herd Situations

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When one speaks of disease prevention, one of the first ideas that comes to mind is vaccinations. While this is an important method, I'd like to come back to this later, as there are more fundamental and important methods to first be considered.

Animals should live in a dean environment. They shouldn't have to lie in their own feces or urine, breathe stale air, or drink dirty water. Infection is often a question of numbers; while the body's own immune system can usually handle a few invading bacteria or viruses, a massive overload will often overwhelm even a healthy individual.

Good nutrition allows all organ systems, including the immune system to function properly. The diet should consist of a wide variety of food stuffs appropriate to each individual species. For most live stock, this consists of a variety of plants and herbs, preferably in a fresh or naturally preserved state, such as in hay or silage. Heating destroys or changes many nutrients and can lead to deficiencies. The best way to ensure that an animal is getting a wide variety of nutrients is to allow it to gaze in a native pasture where, in addition to grass and legumes, it can also consume various herbs. We need to trust an animal's instincts to seek out those herbs and nutrients it needs to heal itself, for what is instinct but the cravings and aversions the body has for certain materials. If the body needs a certain nutrient, the animal will have a craving for that nutrient, and will consume it in g-eater than normal amounts until that need is satisfied. Similarly, an aversion is the body's way of saying that there is something here which is not good, that may be harmful, and so to avoid it. Few animals will eat something poisonous if there is other feed available. Native fields, rather than monocultures, are more likely to have a greater variety of healing herbs.

Low herd densities in a field allow for more choice in the balance of plants consumed. It's easy to determine the carrying capacity of a field and then to stock it under that carrying capacity. This allows both for better nutrition and for better hygiene, as the animals are more able to avoid each others' waste. Pasture rotation furthers this. Following one species on a pasture with another avoids contamination while at the same time allows for better utilization of fields. Goats, for example, browsers, could follow cattle or sheep, grazers, followed by pigs, rooters. Companion animals can help reduce disease too. Guinea fowl, and to a lesser extent chickens, will eat ticks, thus lowering the incidence of Lyme disease.

Most herd animals will go off from the herd when giving birth, thereby avoiding disease and contamination to the newborn. An important start for any newborn mammal is its mothers colostrum, which gives it an early passive immunity to diseases.

Proper hygiene is important to avoid disease. Animals should not be forced to live in their own excrement. By nature, most herd animals are migratory, seeking fresh pastures, and leaving their feces behind. Contact with stool leads to increased worm burdens, as well as disease from Salmonella, E. coli, and other gastrointestinal diseases, and can lead to mammary infections. Contact with urine can spread leptospirosis. Overcrowded barns increase ammonia and water vapor in the air, leading to respiratory infections and immune weakening.

Barns need proper sanitation, where the feces and urine are removed, fresh air is circulated and clean water is provided. Lower population densities mean a lowered likelihood of spreading disease. If the animals can't move away from their wastes, the wastes must be removed from the animals.

Lets look at some specific steps that can be taken to enhance immunity. The first and most important is to ensure that all newborn mammals receive colostrum from their dams. This provides them with antibodies against the disease to which their dams had been exposed. It would be wise to always have some frozen colostrum on hand for those newborn who for some reason didn't get it from their dam. Colostrum can also be used in older animals to treat diarrhea and gastrointestinal dysfunction, as well as providing specific antibodies and general immune stimulation.

There are numerous plants that have the ability to stimulate an animal's immune system. Some, such as Echinacea and golden seal, are well known for vial and bacterial infections. Another common immune stimulant, garlic, also helps to dispel intestinal parasites. Other, less well known plants that will help prevent, and also treat, viral infections are cats claw, astragalus, pao d'arco, thuja, St. John's wort, and various mushroom types such as reishi, shitake, and maitake. Lemon balm is useful for treating as well as preventing herpes infections. This list is certainly not complete, as this is a new and evolving field. Oscillococcinum, from duck liver, is used to stimulate the immune system after exposure to the flu. Most materials that can prevent infectious diseases can also treat them, though the reverse is not always true.

The most common method of specific disease prevention is by vaccination. For many diseases, this is quite effective, but not for all. In other words, the efficacy of the vaccines vary significantly. For example, the rabies vaccine and canine and feline distemper vaccines are very effective, while the feline leukemia vaccine, FIP vaccine, and Lyme disease vaccine are almost worthless. Parvo vaccine is moderately effective, as is the kennel cough vaccine. The other problem with vaccines are the side effects, the most serious of which are long term. Vaccines are designed specifically to stimulate the immune system, leading at times to auto-immune problems. The canine distemper vaccine may lead to hypothyroidism and the feline distemper vaccine to hyperthyroidism. Lyme disease vaccinations have at times induced symptoms of Lyme disease, and Feline Leukemia vaccinations have led to clinical FIP. Rabies vaccinations in older cats and dogs can lead to renal failure.

Homeopaths have found that certain remedies could be given in the face of epidemics which would prevent those epidemic diseases from infecting those patients. Teste relates how Hahnemann first found this in a Scarlet Fever epidemic, where a patient he had previously given Belladonna did not develop Scarlet Fever while all the rest of her family became ill. He later used camphor to protect against cholera. Others have found other remedies protective; lathyrus for polio, mercurius cyanatus for diptheria, and baptisia for typhoid, amongst others.

Other homeopaths found that giving a potentized remedy made from the disease organism or typical infectious agent could protect against that disease. Such a remedy is called a nososde. Hering,1879, protected several dogs from rabies by using a remedy made from the saliva of a rabid dog. Homeopaths have used morbillinum to protect against measles, diphthermnum for diptheria, pertussinum for whooping cough, variolinum for small pox, and tuberculinum for tuberculosis, amongst others, according to Shepherd, 1983.

Clinical trials in recent years by homeopathic veterinarians have yielded interesting results. Day, 1986, in England, used a mastitis nosode to lower the rate of mastitis in a herd of dairy cows,

as well as lower the cell count in the milk. Another clinical trial of Day, 1987, reduced the incidence of kennel cough in a boarding kennel by giving kennel cough nosode, from over 90% to under 5%. Saxton, 1991, also in England, dropped the incidence of distemper in a dog pound from over 11% to under 5%. In a number of catteries, I have reduced the incidence and severity of feline upper respiratory tract infections by giving a nosode made from the discharge of affected cats. I have been using a Lyme disease nosode to protect dogs and horses from Lyme disease, and have seen no more than 10 cases in the 10 years I have been doing this. My own experience with kennel cough nosode is that it will prevent the spread of kennel cough and can also be used to treat kennel cough.

From time to time, new diseases appear, like parvovirus disease in dogs, or appear perhaps in a new locale, such as HIV. Many of these are viral diseases. Developing a new vaccine takes many years, if possible at all. If the infectious agent is known, be it saliva, mucous, blood, feces, or something else, a homeopathic nosode can be made that would very likely b protective against that disease.

Here is how to prepare such a nosode. Let's assume that a major symptom is a nasal discharge, and there is coughing, so it is likely the disease is spread by coughing, spreading aerosols. Get a small 1-oz bottle of vodka, pour off half of it (save this). With a 0-tip, wipe up some of the mucousy discharge from a sick animal. Cut the tip off of the 0-tip so that it falls into the half-filled small vodka bottle. With a fresh 0-tip, wipe mucous from another sick animal. Cut head of Q-tip, wipe mucous from another sick animal. Cut head of a 0-tip off so it falls into the vodka bottle. Repeat with each sick animal. Put the cap back onto the bottle, shake well, and leave for a few days to macerate. Take a small vial, about 10 ml (I use a 10 dose rabies vaccine vial), wash it well, sterilize it, dry it, then add water until it is about half full, counting the number of drops added, until it is an even multiple of 100; that is, 200, 300, 400, etc. Put a piece of clean tape around the vial and with an indelible marker, mark the height of the water level. With a dropper, add 1 drop of the vodka mix for each 100 drops of water in the vial. For example, if you have 300 drops of water in the vial, add 3 drops of vodka mix; to 400 drops, add 4 drops vodka mix, etc. Take some fluffy towels, fold them and pile them up. Put a stopper in the vial, hold the vial in your fist, and pound your fist onto the towels 10 times. This is now your 1 C potency. Take out the stopper, pour out the contents of the vial, immediately stand the bottle upright, (a few drops cling to the wall) and add fresh water up to the mark showing the original water level. Replace the stopper, take the vial in your fist and pound your fist into the pile of towels 10 times. This is the 2C potency. Continue through the 28C potency. This time, to make the 29C potency, don't add water, but use the vodka you originally poured out of the bottle, before you added the 0-tips, to fill the vial to the original water level. Cap it, pound it (called sucussing), but pour this into a small jar and save it. Add some more vodka to your potentising vial to make the 30 C potency. This is what you will dispense. Add 1-2 d-ops to each animal's water bowl or bucket. Try to keep the water bucket out of direct sunlight.

The protocol I generally use is to give the nosode once a day for 1 week, then once a week for 1 month, then once every six months. Some people prefer to give it once a day, especially when there is a continually changing population, such as in an animal shelter. If you think you will be using a lot of the nosode, make your 28C potency also with the vodka and save. When you run out of the 30 C potency, put 100 (tops of water in a vial and add 1 (top of the 29 C potency in vodka, sucuss 10 times, and you have a 30 C potency. This is easy to make, costs no more than a 1

ounce bottle of vodka and a few Q-tips, and in spite of it's simplicity, will amaze you with how effective it is in preventing disease, and even in treating the same disease.

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AVMA Perspectives on Complementary and Alternative Veterinary Medicine

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The AVMA Executive Board convened the Task Force on Complementary and Alternative Medicine in order to review and revise the Guidelines that were created in 1996. There has been an increasing amount of interest in complementary and alternative veterinary medicine (CAVM) at many levels—private practice, some students and faculty at the accredited veterinary colleges, and among legislative bodies in various States and Provinces. In view of this, the Task Force was Charged with the following:

1) Research the literature on the development and use of alternative and complementary therapies in veterinary medicine, including: acupuncture, botanical medicine, chiropractic, holistic medicine, homeopathy, massage, nutraceuticals, and physical therapy.
2) Review the 1996 AVMA "Guidelines on Alternative and Complementary Veterinary Medicine" in the light of current literature and knowledge about the application and efficacy of the alternative and complementary therapeutic methods.
3) Recommend to the Executive Board revisions to the Guidelines that are necessary to make them consistent with the current knowledge in the subject areas to provide up-to-date guidance for AVMA members.
4) Review and report on programs designed to provide opportunities for providing education to members of the veterinary profession on the application and efficacy of alternative and complementary therapies.

Chosen to be members of the Task Force were AVMA members representing the following sectors of the profession. Each sector or species organization sent nominations to the Executive Board, which then chose one person per sector.

1) Equine practice (only traditional Western medicine)
2) Equine practice (using CAVM as well as traditional Western medicine)
3) Small animal practice (only traditional Western medicine)
4) Small animal practice (using CAVM as well as traditional Western medicine)
5) Food animal practice
6) Academic clinician
7) American Association of Veterinary State Boards (AAVSB)
8) Association of American Veterinary Medical Colleges (AAVMC)
9) AVMA Executive Board—serving as Chair of the Task Force

The names of the individuals are being kept confidential at this time (except Drs. Harman and Karreman present at this meeting) until the process is complete. In the last two weeks the Task Force reached unanimous agreement regarding the document and the Chairman has moved the process forward—submitting the document to the AVMA Executive Board for review. It is anticipated that the Executive Board will be sending the document out for comments, either to the AVMA membership in its entirety or to all known veterinary groups (both traditional Western oriented and alternative) for each group's official response.
Once unanimous agreement was reached, the Chairman generated a list of anticipated Frequently Asked Questions (FAQ's), to which the Task Force members are still adding, deleting and/or creating answers. These are (so far):

1) Why are guidelines for CAVM needed?
2) How were these guidelines developed?
3) Why are the definitions and descriptions of some specific CAVM modalities in the 1996 AVMA Guidelines for Alternative and Complementary Therapies missing from these guidelines?
4) Do these guidelines support or discourage CAVM?
5) Do these guidelines establish a different standard for CAVM than that for other medicine?
6) Do these guidelines support the practice of CAVM by non-veterinarians?
7) What training is needed to become competent in CAVM?

It is hoped that we (Drs. Harman and Karreman) will be helpful in interpreting this meeting's information in light of the work done by the AVMA Task Force on Complementary and Alternative Veterinary Medicine.