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Dr Emanuel REVICI
Selenium vs Cancer

http://drrevici.com

Dr. Emanuel Revici

The Einstein of Medicine

Emanuel Revici, MD transformed medicine in the 1930's during the laboratory and clinical research he conducted in Paris. By observing the quantum or energetic properties of lipids in health and disease, Dr. Revici discovered non-toxic lipids that treat pain and cancer. Thereafter he pursued his research at the Institute of Applied Biology in Mexico and NYC until his death in 1998 at 101.

Dr. Revici was always 50-100 years ahead of his time. While physicians and scientists have confirmed some of his discoveries in the last sixty years, many remain unrecognized. Once tapped however they stand to transform medicine in the 21st century.

The Doctor Who Cures Cancer

This is the story of Emanuel Revici M.D., his groundbreaking medical discoveries and his success in treating pain, cancer and other illnesses with his non-toxic "chemotherapy". It is a true story of a physician whose work was published by the prestigious Pasteur Institute, yet who was subsequently persecuted and prosecuted by the medical establishment. Kelley Eidem captures a genuine feeling of this extraordinary physician often told through the experiences of Dr. Revici's patients. This story will melt your heart.

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http://www.healthy.net/Health/Article/Revici_Therapy/2013/3

(Excerpted from Options: The Alternative Cancer Therapy Book ; ISBN: 0895295105; Published by Avery Publishing, New York)

Cancer: Revici Therapy

by

Richard Walters

Dr. Emanuel Revici has developed an original approach to the treatment of cancer. His nontoxic chemotherapy uses lipids, lipid-based substances, and essential elements to correct an underlying imbalance in the patient's chemistry. Lipids-organic compounds such as fatty acids and sterols-are important constituents of all living cells. They are a separate, critical system in the body's defenses against illness, according to research conducted by Dr. Revici early in his career.

The Romanian-born physician, who practices in New York City, has applied his wide-ranging discoveries for over sixty years to the treatment of cancer as well as many other disorders, including AIDS, arthritis, Alzheimer's disease, chronic pain, drug addiction, schizophrenia, allergies, shock, and burns. The great majority of his cancer patients are in advanced stages of the illness. Five, ten, sometimes twenty years after receiving treatment, some of these patients are in remission with no signs of active disease.

Revici, in his mid-nineties, is fiercely dedicated, still makes occasional house calls, and has patients call him at home. To critics, his approach is far too complex, too theoretical, and inconsistent in its results. Even friendly critics within the alternative health field say he cures very few cancer patients. But to admirers, he is a man who has saved the lives of cancer patients pronounced hopeless by orthodox doctors, a scientific genius who has opened up whole new vistas and whose theories and discoveries may serve as a principal basis for future medicine.

Commenting on Revici's 1961 book, Research in Physiopathology as a Basis of Guided Chemotherapy With Special Applications to Cancer, Dr. Gerhard Schrauzer a leading authority on selenium, wrote, "I came to the conclusion that Dr. Revici is an innovative medical genius, outstanding chemist and a highly creative thinker. I also realized that few of his medical colleagues would be able to follow his train of thought and thus would be all too willing to dismiss his work."1

Dr. Revici views health as a dynamic balance between two opposing kinds of activity that occur in all living systems. One process, the anabolic, or constructive, fosters the growth and build-up of natural patterns. The other process is catabolic, or destructive, involving the breakdown of structure, the liberation of energy, and the utilization of stored resources. According to Dr. Revici, a long-term predominance of either activity leads to abnormality and disease.

In his "guided 1ipid" therapy with cancer patients, Revici has found two basic patterns of 1ipid imbalance-one, the result of an excess of sterols, and the other, the result of an excess of fatty acids. Sterols are solid unsaturated alcohols such as cholesterol. In treating cancer, Revici first determines whether the anabolic or catabolic phase of activity is currently

progressing unchecked. Then he administers lipidbased compounds to renormalize the balance between the body's opposing forces.

Revici describes the body's overall defense system as consisting of four successive phases. When an antigen, or foreign substance, such as a virus or microbe, enters an organism, it activates the defense system. In the first phase, the antigen is broken down by enzymes. This is followed by the lipidic phase, followed in turn by the coagulant antibody phase, and succeeded finally by a phase mediated by globulinic antibodies able to fully neutralize the antigen.

The key point about this defense system is that a new phase does not start until the previous phase has been successfully completed. At any point where the agents available are qualitatively insufficient to defend against the noxious influence, the sequence breaks down. Then the body overcompensates by manufacturing excessive amounts of the defense agents from the breakdown point, and it does not progress to the next phase. Revici found that most chronic diseases, including cancer, are characterized by such abnormal conditions. When the body's defense is arrested in the lipidic phase, either fatty acids or sterols are produced in abnormally large quantities, leading to a variety of disorders, including cancer.

Patients diagnosed with an excess of sterols are treated with fatty acids to correct the imbalance. Conversely, patients found to have a predominance of fatty acids are treated with sterols and other agents.

This "biologically guided chemotherapy," as Dr. Revici calls it, is highly individualized to suit each person's specific metabolic character and condition. "There are simply no two cancers which are alike, just as no two individuals are alike," he has said.2 The substances and dosages used are unique for each patient and can be changed if analytical tests reveal a change in the body's balance. Through regular tests, such as the urine pH, specific gravity, surface tension, and chloride index, Dr. Revici can detect systemic changes in the body produced by lipid imbalances.

Revici's research has demonstrated that lipids have an affinity for tumors and other abnormal tissues. Because of this, the lipids or lipid-like synthetic compounds administered to the patient, either by mouth or injection, travel directly to the tumor or lesion. Cancerous tissue is abnormally rich in free lipids, and the lipidic agents introduced into the bloodstream are readily taken up by the tumor.

Revici's nontoxic cancer therapy has been denied both fair testing and funding in the United States, though it has been studied and put into practice in France, Italy, and Austria. A distinguished physician and research scientist who graduated first in his class at the University of Bucharest, Dr. Revici has been stereotypically portrayed by the American media as a quack who should have been put out of business a long time ago. The American Cancer Society put Revici's therapy on its Unproven Methods blacklist in 1961, and in 1984, the State of New York tried to revoke his medical license permanently on grounds of deviation from standard medicine, negligence, incompetence, fraud, the use of unapproved experimental drugs, and similar charges. After four years of struggle, Revici triumphed in duly 1988 with a decision that placed him on probation but allows him to continue treating cancer patients.

To save his license, Revici's patients and several medical civil-liberties groups undertook

intensive lobbying at the state capitol. At the federal level, New York Congressman Guy Molinari held an all-day hearing in March 1988 to address the Revici matter and the whole field of alternative cancer therapies. Dr. Seymour Brenner, a respected radiation oncologist in private practice in New York, testified on Revici's behalf He had investigated a number of patients in very advanced stages of cancer, incurable by orthodox means, whom Revici had put into long remissions. Dr. Brenner had an independent panel of pathologists confirm the diagnosis and stage of illness prior to each patient's initial visit to Revici. He testified that his personal findings strongly suggest Revici has a cancer treatment deserving further study, and he proposed that such an evaluation be conducted by the FDA.

…In a letter to Congressman Molinari, Brenner outlined a protocol in which a panel of doctors would monitor cancer patients placed on alternative therapies after their conditions had been deemed unamenable to the standard forms of treatment. The letter contained the detailed case histories of ten advanced cancer patients whom Revici had healed.

One patient, a forty-three-year-old man, was diagnosed with an invasive, high-grade cancer of the bladder at Memorial Sloan-Kettering Cancer Center in September 1980. "They said, 'The only way you can be treated is if we take your bladder out and give you a colostomy on the side.' He said no.", The patient visited Dr. Revici in October and went on the therapy. He has had no other treatment. In 1987, he returned to Sloan-Kettering for a cystoscopy, which revealed him to be cancer-free.

Another patient, a twenty-nine-year-old woman, was operated on at Memorial Sloan-Kettering in October 1983 for a chordoma, a brain tumor. The tumor was incompletely resected, and the patient was given a course of radiation therapy. The young woman's condition progressively worsened during the twelve months following surgery. She was seen by Dr. Revici in May 1984, at which time she was confined to a wheelchair, with limited function. Since she started the Revici program, she has had two babies and functions well. Her only problem is that she walks with a cane.

Marianne Dimetres achieved remission from preterminal uterine cancer through a combination of Revici's nontoxic medications, wheatgrass therapy, diet, and psychological support. See her story on page 157.

Revici, who holds patents for his numerous chemical compounds, claims to have devised a novel technique to open double bonds in molecules of unsaturated fatty acids in order to incorporate different metallic elements at precise points in the molecules. The result is an entirely new series of therapeutic compounds, exceedingly low in toxicity and incorporating selenium, copper, sulfur, zinc, calcium, nickel, beryllium, mercury, lead, and other elements. In general, these compounds reportedly have a toxicity less than one-thousandth of that of the elements in the forms normally available. The technique converts toxic substances into safe anticancer agents. "Through this method, Revici has opened up an entirely new field for the therapeutic use of these elements," according to Dr. Dwight McKee, one of Revici's medical associates.4

Revici's use of selenium in the treatment of cancer predates mainstream interest in this mineral by more than twenty years. Selenium is one of the major trace elements always found deficient in cancer-prone populations. Research has shown that it is of value not only in preventing cancer but also in treating it. Revici uses a special molecular form of selenium (bivalent-negative selenium) incorporated in a molecule of fatty acid. In this form, he can

administer up to 1 gram of selenium per day, which corresponds to 1 million micrograms per day, reportedly with no toxic side effects. In contrast, too much selenite (hexavalent-positive selenium) has toxic effects on animals, so human intake of commercial selenite is limited to a dosage of only 100 to 150 micrograms by mouth. Dr. Revici often administers his nontoxic form of selenium by injection, usually considered to be four times more powerful than the form given orally.

Extra selenium in the diet drastically reduces the spontaneous occurrence of cancer in mice. In human populations, high selenium intake correlates with low cancer rates. In a 140-~patient study of cancer victims treated with selenium, Dr. R. Donaldson of the St. Louis Veterans' Administration Hospital reported in 1983 that some patients deemed terminal with only weeks to live were completely free of all signs of cancer after four years; all the patients showed a reduction in tumor size and in pain.5

Dr. Revici uses the Periodic Table of Elements as one of several guides when choosing the best course of treatment for a patient. This ties in with his view that cancer is part of a hierarchical organization found throughout Nature, from the precellular level to the entire organism. All the known elements, in his view, can be classified as supporting either anabolic or catabolic activity, and each element's biological activity correlates with its position in the Periodic Table. Revici maintains that the vertical rows in the table all share either anabolic or catabolic activity, whereas the horizontal rows indicate at which level of biological organization a particular element acts-whether at the level of a subnuclear particle (nucleoprotein), nucleus, cell, tissue, organ, or whole body. By this means, Dr. Revici determines the body level (or levels) most affected by the illness and therefore most in need of therapeutic intervention. This information is correlated with diagnostic tests indicating which imbalance is present at which level.

Harassed for decades by the American medical monopoly, Revici, ironically, had originally come to the United States seeking freedom to do his work. A scientific prodigy, he had written his first research manuscript at the age of twelve and entered the University of Bucharest at seventeen. In 1936, after serving as an assistant professor on the Faculty of Medicine, he moved with his family to Paris, where he spent three years investigating the biochemistry of cancer. When World War II erupted, the Revicis fled to Nice, where the doctor joined the French Resistance and gave medical aid to wounded Resistance fighters sought by the Nazis. His anti-fascist activities so endangered him and his wife and daughter that the leaders of the French Underground had to arrange for the family's passage out of Europe.6 The Revicis settled m Mexico, where Dr. Revici founded the first Institute of Applied Biology, in Mexico City.

Eager to advance his research in the United States, Dr. Revici was granted three special visas through the intercession of Sumner Welles, a special aide to President Franklin D. Roosevelt.7 Revici moved to Chicago, then to New York, establishing the institute anew in Brooklyn in 1947. Today, his office is located in a two-story building in Manhattan, where he treats patients aided by a small support staff.

By 1948, Revici had begun exploring the use of selenium in treating cancer and as a means for rendering radiation less harmful. His promising findings on radiation came to the attention of United States Navy scientists testing A-bombs in the Pacific. Twice, the scientists invited him to join them in studying radiation's harmful effects.

In 1954, Revici's fund-raising organization financed the purchase of Beth David Hospital in Manhattan. Renamed Trafalgar Hospital, this general-care facility employing over 200 resident and visiting physicians enabled Revici, as the chief of oncology, to provide round-the-clock care for critically ill patients. Its animal research laboratories were staffed by 35 scientists and technicians, all involved in projects related to Revici's theories and therapeutic approach. Revici served as chief of Trafalgar's oncology department for over twenty years. The hospital dosed in 1978 due to financial difficulties.

Revici's treatment agents were used in Belgium with favorable results by Professor Joseph Maisin, president of the International Union Against Cancer and director of the Cancer Institute of the University of Louvain. Between 1965 and his death from a car accident in 1971, Maisin corresponded with Revici to describe how he treated patients with advanced metastatic cancer who had failed conventional therapies. Maisin used several Revici preparations, at times coupled with low-dose radiation. He reported that in nine of the twelve terminal-cancer patients on the Revici medicines, significant improvements occurred, including regression of tumors, disappearance of metastases, and cessation of hemorrhage. Incredibly, paralyzed patients were able to walk again.

Dr. Revici developed successful treatments for heroin and alcohol addiction. His detoxification agent for heroin addicts, called Perse, was almost chosen over methadone as the nation's treatment of choice. Perse, which incorporated selenium in a lipid base, physically detoxified addicts within five to eight days. At the request of Congress, Revici presented over 2,000 case histories of successful uses of this nontoxic and nonaddictive agent. The idea for Perse had arisen from Revici's cancer practice after he observed that patients previously on addictive narcotic analgesics exhibited no withdrawal symptoms when placed on his lipid analgesics.

At a 1971 congressional subcommittee hearing that took testimony about Perse for a full day, Congressman Charles Rangel of New York said, "The results and what we witnessed with patients was so unbelievable that the doctor from Municipal Hospital has now gone back on a daily basis in order to continue with this chance to see the miraculous results that have taken place."

Barron's ran a full-page feature on Revici's treatments for narcotic and alcohol addiction in 1972. Both Congress and the FDA promised Dr. Revici full support for large-scale clinical testing, signaling that Perse could be the most important breakthrough in drug treatment. Because selenium is normally toxic in high doses, Revici reformulated the medication to eliminate it. The new substance, called Bionar, worked just as well-in the same amount of time, with no withdrawal symptoms. (The selenium incorporated in Perse was a bivalent-negative form, very active and virtually nontoxic.)

The stage seemed set for a major advance in the war on drugs. But less than one month after the congressional hearing, the FDA reversed its position and recommended methadone, an addictive and toxic drug, as the treatment of choice. Why?

One possible answer is provided by Marcus Cohen, who helped coordinate the campaign to save Revici's license. He suggests, "Hospitalization was required for treatment with Perse, and because many of the patients were poor, Medicaid was asked to pick up the tab. As in the case of most drug addicts, they presented with other conditions besides addiction which needed medical attention.... Methadone, addicting in itself, nevertheless was favored by State

and City officials as a means of controlling the mostly black and Hispanic drug population.... The drug companies and health care professionals that profited from exclusive use of methadone did not welcome competition, least of all from a treatment which did not cause a lifelong dependency."8

Dr. Revici's nontoxic treatment for AIDS applies his findings on the antiviral and immune-enhancing properties of certain lipids. He views AIDS as a "quadruple pathological condition," consisting of:

1. a primary viral infection, inducing
2. a deficiency in the body's natural lipidic defense, followed by
3. secondary opportunistic infections or specific neoplasms (cancers)
due to the lack of certain lipids, resulting in
4. an exaggerated imbalance, usually catabolic.

Each of the four conditions is addressed with a specific therapeutic approach. Antiviral agents are given to inactivate, or kill, the human immunodeficiency virus (HIV). To counteract the patient's nonspecific loss of defense against opportunistic infections, Dr. Revici administers, via injection, a group of phospholipids that he calls refractoriness lipids. These compounds appear to induce a generalized resistance (refractoriness) toward many different antigens. The doctor claims impressive results with these preparations in the clinical manifestations of AIDS and AIDS Related Complex (ARC). Antibiotics are also given to combat the secondary opportunistic infections. To redress bodily imbalances, the appropriate anticatabolic or antianabolic agents are used.

Two of Revici's therapeutic compounds for cancer, amyl selenide and tri-thioformaldehyde (TT), tested positive in trials conducted in the late 1970s by the National Cancer Institute and Roswell Park Memorial Institute.9 Another selenium compound that Revici developed showed activity against four tumor systems in tests conducted in England. However, the dose at which antitumor activity was found was "fairly close to the toxic dose," and further studies of the compound were recommended.

An unpublished study of the 1,047 cancer patients treated with the Revici regimen between 1946 and 1955 was made by Robert Ravich, M.D., who worked closely with Revici. Most of the patients were far advanced or terminal, and most had prior conventional treatment. Of the 1,047 cases, Ravich found that 100 had favorable response (objective and subjective); 11 had objective response only; 95 had subjective response only; 296 showed no response; and 545 had equivocal or undetermined response (380 of this last group were treated for less than three months).10

The only published clinical study of Revici's treatment for cancer appeared in the Journal of the American Medical Association JAMA) in 1965. It was written by a panel of nine New York physicians after Revici himself requested that a scientific panel review his cancer-management program. After two years of observation, the panel concluded that the Revici therapy was "without value." The authors reported that 22 of the 33 patients in the study died of cancer or its complications while on the Revici treatment and 4 more died after discontinuing the regimen. None of the 33 showed signs of objective tumor regression, according to the authors.

Dr. Revici wrote a detailed rebuttal in which he stated that the panel had ignored evidence

indicating several tumor remissions, multiple reductions in tumor size, and relief of pain in many advanced patients. He noted that of the nine physicians on the panel, only two had actually seen the patients during the entire two-year study. He further commented that he had requested the study in the "hope that the demonstration of positive results in even a few of these advanced cases would excite sufficient interest to lead to a large-scale study of our approach.... To conclude from a limited study, such as this, that the method should be discontinued, in all cancers, is to say that since surgery and radiation have failed in these same terminal patients, these 'recognized' methods should also be discontinued, not only in these types of cancer but in all cancers in general." Although Dr. Revici submitted substantiating pathological data in his lengthy rebuttal,JAMA refused to publish it.

It is now more than forty years since Revici developed his nontoxic chemotherapy. An open-minded, unbiased evaluation of it is long overdue.

References

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6. Marcus A. Cohen, "On Emanuel Revici, M.D.," unpublished manuscript, 1988.
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http://www.oncolink.org/treatment/article.cfm?c=171&id=565

The Revici Method for the Treatment of Cancer

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The Revici Method is an unconventional therapy for the treatment of cancer developed by Emanuel Revici, MD. Dr. Revici believed that pathologic conditions were due to a chemical imbalance within the body that could be modified. The method is a blending of clinical observations, laboratory analyses, and chemotherapy. Basically, Dr. Revici would analyze the urine, blood, and body temperature and place patients in specific categories based on the "imbalance" that was discovered from these tests. The method was analyzed by a Clinical Appraisal Group consisting of a number of prominent physicians in the 1965. Thirty-three patients treated by Dr. Revici were analyzed by the group of physicians. No instance of objective tumor regression was observed in any of the 33 cases studies. In fact, 15 patients

had autopsies after their deaths and there was no evidence of tumor alteration as a consequence of therapy.

Dr. Revici remained embattled with the New York State health authorities for years and had his medical license was revoked in 1993 at the age of 96. Although Dr. Revici has died, his method remains highly touted in unconventional medical therapy books and on the Internet. In fact, a number of therapies that closely resemble the Revici Method are now being touted by unconventional medical practitioners.

Biologic Terrain Assessment (BTA) is a therapy that is remarkably similar to the Revici Method and promoted by some alternative medicine practitioners. It utilizes an analysis of the saliva, urine, and blood to isolate "imbalances". Herbal therapies are then prescribed to counteract these imbalances. In fact, practitioners of BTA claim that the herbal treatment can be directed to the organ containing the cancer to make it more effective. There is no objective evidence that BTA has any impact on cancer. There are no scientific studies evaluating its effectiveness. Some unconventional practitioners continue to claim effectiveness has been proven based on case reports and testimonials, which are not valid scientific endpoints.

OncoLink does not recommend patients utilize the Revici Method or Biologic Terrain Assessment. Any patient considering an unconventional medical therapy should discuss this with their conventional medical physician. There can be important interactions with conventional cancer therapy or side effects of the therapy that you may not be aware. For more information on unconventional medical therapies and cancer see OncoLink's Complementary Treatments section.

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http://thatcrazypharmacist.com/?p=670
June 15, 2011

Emanuel Revici's Book – 'Research in Physiopathology As Basis of Guided Chemotherapy – With Special Application To Cancer'

This book was written by Dr Revici to explain his theories and to show results of his cancer treatments. You can read the online version here:

http://babel.hathitrust.org/cgi/pt?seq=5&id=mdp.39015003770982&page=root&view=image&size=100&orient=0

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http://onlinelibrary.wiley.com/doi/10.3322/canjclin.39.2.119/pdf

The "biologically guided chemotherapy" used by Emanuel Revici to treat cancer and many other conditions is based on his theory..

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http://www.orthomolecular.org/library/jom/1988/pdf/1988-v03n01-p003.pdf

...jury acquitted Dr. Revici of any claims of fraud or lack of ... to find malpractice if Dr. Revici's therapy was not .... 1987). The attorneys for Dr. Emanuel Revici.

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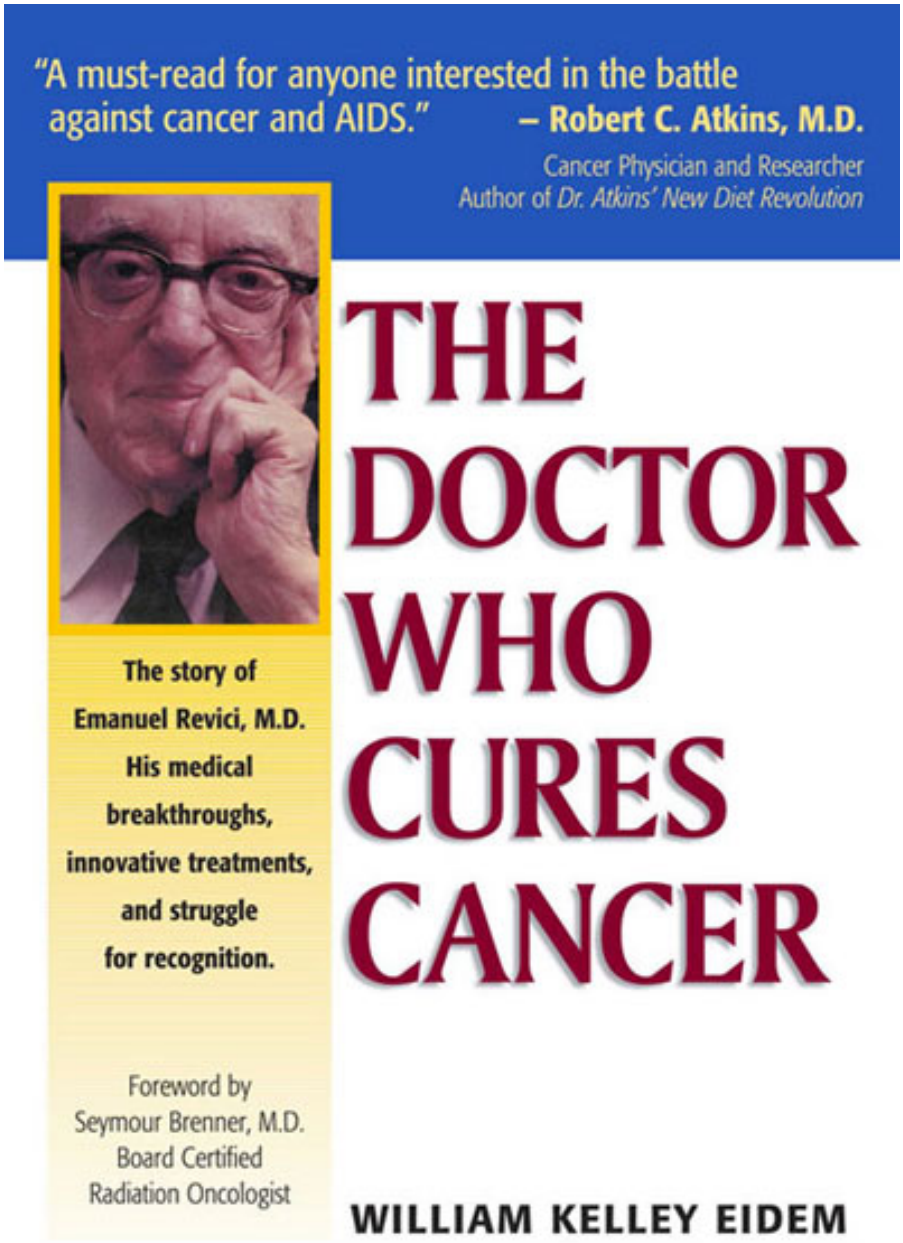
https://www.amazon.com/Doctor-Who-Cures-Cancer/dp/1438263902

The Doctor Who Cures Cancer

by

William Kelley Eidem



The controversial Emanuel Revici, M.D., made the bones grow back in cancer patients, and restored health to AIDS patients as well as drug addicts and alcoholics. His medicines lifted debilitating migraines in as little as 3 minutes. Revici's reward? He was attacked and ostracized by the best. JAMA published false reports about his work. The American Cancer

Society blasted him time and again. Meanwhile, word of mouth brought new patients to see him for decades. The smears didn't work, so something more needed to be done. This is the true story of the greatest medical scientist who has ever lived. Find out what happened to Dr. Revici and find out how you can use the principles of his discoveries to reverse even advanced cancers and many other illnesses.

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http://www.espacenet.com

PATENTS

PHARMACEUTICAL COMPOSITIONS HAVING ANTINEOPLASTIC ACTIVITY ZA8401714

SPECIFICATION

Pharmaceutical compositions having antineoplastic activity The present invention refers to pharmaceutical composition having antineoplastic activity, containing as 5 active principle a combination of the following compounds:

a) bivalent negative selenium in form of selenium incorporated in "tung oil" or of diselenide of formula R-Se-Se-R, wherein R is an alkyl or alkenyl group having an odd number of carbon atoms.

b) an allphatic carboxylic acid, aldehyde or ketone having an odd number of carbon atoms.

Another object of the invention is provided by pharmaceutical compositions containing, in addition to said 10 compounds and to suitable excipients, also other agents endowed with complementary activities, synergistic or able to decrease the side effects.

The antitumoral and antineoplastic activity of selenium derivatives has been already described in the european patent application n. 83104923.4 of May 19,1983 (publication number 0095663).

From a clinical and pharmacological point of view, the compound obtained by reaction of elementary selenium and eleostearic acid (main constituent of tung oil), whose action can be enhanced by the contemporaneous administration of extracts of Bixa orellana seeds, proved to be particularly active.

It has now been found that the contemporaneous administration of carboxylic acids, aldehydes or ketones having odd number of carbon atoms is able to decrease the side effects induced by selenium and allows therefore to increase the dosage.

Also substances such as alcohols or polyalcohols, some amine compounds and corticosteroids which turned out to be active in decreasing the side effects, can be optionally present in the compositions according to the invention.

The odd number of carbon atoms is preferably from 5 to 9. The aliphatic group or groups present preferably comprise alkyl groups. Ketones are preferred, especially those in which the

keto group is between 25 alkyl groups each of which has an even number of carbon atoms.

Preferably, 3-heptanone, 3-pentanone, 3 or 5-nonanone, in combination with propyl, penty], heptyl, nonyl or undecyl diselenide, are used.

The composition according to the invention can also comprise lipophilic vehicles, such as sesame oil or the like. The relative proportions of the a) and b) constituents in the pharmaceutical compositions according 30 to the invention may range from 1: 10 to 1:50.

Other substances which can be present according to the invention are polyalcohols or alcohols having odd number of carbon atoms, preferably glycerol, aminoalcohols, nicotinic acid, aminobenzoic acids, cortisone.

Preferred composition comprise constituent a) (diselenide) and ketone b) (3-heptanone) in the weight proportions of 1:25 for the parenteral administration and of 1:40 forthe oral one.

The diselenides according to the invention are prepared with known methods while for the preparation of the reaction product of elementary selenium and eleostearic acid or tung oil, reference is made to the previously cited european patent application.

As far as the compositions of the invention are concerned, the following, non limiting examples are reported.

EXAMPLE 1

Vials for intramuscular injection Dipentyl diselenide 3-Heptanone Sesame oil 2% 50% 48% The above composition is distributed into 1 mi vials to be administered by intramuscular route.

EXAMPLE 2

Gelatine capsules or drop for oral route Dipentyl diselenide 55 3-Heptanone Sesame oil 2% 80% 18% 0,5-2 MI of the above composition are dosed in gelatine capsules. Alternatively, the same composition can be directiv administered as drops.

The acute and subacute toxicity of the composition of the Example 1 have been determined by the 60 subcutaneous and intraperitoneal route in mice, rats and dogs.

2 GB 2 135 885 A 2 Acute toxicity The LD50 of the composition of the Example 1, after administration both by subcutaneous and intraperitoneal route, in FC, mice (28-32 g) and in Carworth rats (150-170 g) proved always to be higher than 350 mg Selkg or than 100 milkg.

Subacute toxicity The su bacute toxicity has been studied by administering the composition of the Example 1 by subcutaneous route to Carworth rats (150-170 g) for six weeks (5 days a week) at doses ranging from 10.5 to 350 mg/Se/kg or 3- 100 ml/kg. No death was noticed in any group during treatment.

After the animals' sacrifice, 20 or 40 days after treatment, the microscoptic, hematologic and hematochemical exams did not show any pathological change.

Subacute toxicity in dogs Two groups of 6 Beagle dogs were treated with 0.60 and 1.26 mi/kg of the composition of Example 1 five days a week for five weeks. No death occurred. After sacrifice at the end of the treatment, the pathological 15 and biochemical exams did not show any pathological change.

The compositions according to the invention exert an antineoplastic activity similar to those of the already mentioned european application, such activities being sometimes enhanced because of the high elenium dosages attainable with the compositions of the invention.

The compositions of the invention can be used in clinical medicine in a variety of neoplastic conditions, at 20 dosages ranging from 5-20 g by oral route and from 0.5 to 2 mi by intramuscular route, 2 to 4times daily.

The treatment is based on the concept of a primary subnuclear anomaly and of an abnormal lipidic dualism: the number of eosinophils in blood, the pH, the specific gravity and the surface tension are the most important guide parameters for the treatment.

(The concept of anabolic-catabolic dualism, and relative definitions, are widely illustrated - also from an 25 experimental point of view (in animal and in human field) - in E. Revici, Research in Physiopathology, ediz.

Van Nostrand, Princeton 1961). Nevertheless, the validity of the invention should not be considered as based on the actual verification of the theoretical considerations discussed in said treatise.

Tung oil compositions and use for treatment of body deficiencies US4851437

Various tung oil or tung oil fatty acid compositions and use thereof for treating at least some symptoms of body defense deficiencies in patients having said symptoms.

TECHNICAL FIELD

The present invention concerns various tung oil compositions and their use in methods for treating and preventing the symptoms of different body deficiencies.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I have found that the abnormal in general results from the incapacity, qualitative or quantitative, of the body to resolve the problem resulting from the intervention of a noxious action. I have found that this deficiency concerns the incapacity of the body defense to fight successfully the occuring condition related to the intervention of lipids, and for certain conditions, more specifically of agents having in their molecules a trienic conjugated formation.

I have found that the naturally very efficient defense agents concern fatty acids which have in their molecule three trienic conjugated double bonds formation, respectively three double bonds separated by single bonds. The parallel position of these conjugated trienes especially

when part of a fatty acid gives the agent a marked efficient defense activity.

I have found that a such fatty acid represented by the eleostearic acid, is naturally present in tung oil (china wood oil) obtained from the seeds of Aleuritis Cordata. I have found that the use of the tung oil itself, with esters of this acid and also with other fatty acids present represents an active, and in the same time, an especially favorable accepted form to be administered.

The study of the pathological conditions has shown that a fatty acid defense deficiency is exhibited by a large number of them. They are specifically indicated for the administration of the tung oil. The following pathological conditions and their symptoms represent conditions with such a trienic fatty acids deficiency that can be treated accordingly to the invention: neoplastic diseases such as cancer, sarcoma, lymphoma and leukemia; infections, microbial, fungal and especially viral as in Ebstein - Barr, AIDS, the common cold, influenza and herpes; pain, especially acid pain; aging; arteriosclerosis; hypertension; organ inflammatory conditions convulsions and epilepsy; certain allergies; constipation; manic manifestations and schizophrenia. This enumeration is not limitative, any pathological condition with an anabolic-constructive imbalance representing a special indication for this treatment. In view of the nature of the treatment, according to the invention, the addition of other fats or fatty acids, especially those from polyunsaturated oils, enhances the activity of the tung oil.

The association of these polyunsaturated oils or their fatty acids with the tung oil or its ester compounds, through a common activity represents a progress in their use. Safflower oil, corn oil, cod liver oil, sardine and salmon oils, their fatty acids or other unsaturated fatty acids added to the tung oil enhances its defense activity The eleostearic acid or its salts or esters and the tung oil fatty acids obtained from the tung oil through any procedure are other forms of returning to the body the missing defense lipids which cause the deficiency.

The basic nature of the intervention through an induced natural defense has led to the administration of the agents of this invention also for the general prevention of a diversity of conditions resulting from their deficiency. Cancer, arteriosclerosis and aging represent the main conditions considered to be prevented by the agents of the invention.

The main defect of the use of tung oil, its compounds, its fatty acids, or the eleostearic acid is the induction of diarrhea. The administration by injection reduces this problem, but does not prevent it, especially at higher dosages. The addition of commonly available antidiarrhea preparations, especially those limited to a local intestinal action, may permit the use of higher doses, especially for the administration by injection. The addition of the tung oil of other antianabolic compounds especially indicated for the condition treated, is manifestly enhancing its favorable action. Such compounds comprise mainly bivalent negative selenium, bivalent negative sulfur, 3-ketones, fatty acids, fatty aldehydes, with or without copper, barium and magnesium incorporated therein. This enumeration is not limitative.

In view of the relationship between defense and the agents of the invention, good effects were seen also in conditions with opposite catabolic imbalance, especially when treated together with anticatabolic agents, especially non sterolic. The oxidation of the tung oil may even enhance its activity

The toxicity studies - acute, subacute and chronic in mice, rats, guinea pigs, hamsters and rabbits has shown an acceptance of doses between 500 and and 2000 times higher than those

respectively taken by humans, which represents a fairly good condition. No pathological changes and no carcinogenic action were seen.

The usual doses for the different conditions vary according to the condition, with usual daily doses orally and by injection, from 50 mg of the oil to more than 500 mg. These doses are generally administered twice a day or more frequently, if necessary.

The administration of these formulations are in general limited by the appearance of diarrhea. Due to the unique mechanism of intervention, through the induction of the main natural defense, the inventions opens a new, very broad way in prevention and therapy.

The following examples illustrate the invention. The percentages shown are by weight.

EXAMPLE 1
Tung oil 20%
Safflower oil 80%
For oral administration: 50 mg to 500 mg oil
mixture per dose given twice per day

EXAMPLE 2
Tung oil 5%
Safflower oil 95%
Sterile for injection: same amounts as Example 1.

EXAMPLE 3
Tung oil fatty acid 20%
Corn oil fatty acid 20%
Safflower oil 60%
For oral administration: same amounts as Example 1.

EXAMPLE 4
Tung oil fatty acid 5%
Safflower oil 95%
Sterile for injection: same amounts as Example 1.

While it is apparent that the invention herein disclosed is well calculated to fulfill the objects above stated, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art, and it is intended that the appended claims cover all such modifications and embodiments as fall within the true spirit and scope of the present invention.

Method for relieving pain or producing analgesia
US4695583

A method for treating a host for inducing relief of pain or anesthesia which comprises administering hydrolyzed epichlorohydrin, magnesium thiosulfate, or a butanol at the site of the painful area.

TECHNICAL FIELD

This invention relates to methods and preparations for relieving pain or producing analgesia.

BACKGROUND ART

A number of methods exist for treating pain: an example being U.S. Pat. No. 3,898,325. The applicant has found a new method is particularly effective for this purpose in compositions which are relatively simple to prepare and administer.

SUMMARY OF THE INVENTION

It has now been found that by administering various agents, such as hydroyzed epichlorohydrin (i.e., 1-chloro 2,3-epoxy propane), magnesium thiosulfate, or n-butanol directly to the painful area of a host will relieve the pain or produce analgesia therein.

DESCRIPTION OF THE INVENTION

It is known that the manifestation of pain is observed at the so-called trigger points. To successfully treat such pain, the administration of the compounds of the invention, preferably by injection, is found to control the pain in the immediate area as well as in the entire affected region.

One embodiment of the invention relates to the injection of from 1 to 10 ml of a solution of between 0.1 and 1.5 weight percent hydrolyzed epichlorohydrin at the trigger point or immediate painful area. The epichlorohydrin can be hydrolyzed by heating it in water. These amounts have been found to be advantageous, but can be higher or lower if desired. For example, up to 50 ml of a 0.5 weight percent solution can been used for exceptionally severe cases.

Generally, the pain is relieved in minutes following the injection. If necessary, the injections may be repeated, preferably 1-2 days later. If a stronger pain is present the next day at the site of the injection, this may be the result of an local inflammatory reaction. When this occurs, the pain usually disappears the day after, and the long term results are generally better.

Another approach for relieving pain is based upon the fact that pain generally has either an acid or alkaline pattern. This character is recognized through a relationship with the urinary pH: the acid pain being stronger with a lower pH and being weaker with a higher pH. The alkaline pains is just the opposite.

The acid pain corresponds to an anabolic imbalance with the predominant pathogenic action caused by steroids, while the alkaline pain corresponds to a catabolic action, with the predominant pathogenic action caused by fatty acids.

Many different agents can be used to counteract these imbalances. For the anabolic imbalances which are evidenced by acid pain, the injection of a solution of magnesium thiosulfate is utilized. The amount of this solution includes between about 10 and 50 ml of a water solution containing between about 10 and 50 weight percent magnesium thiosulfate.

For alkaline pain, which indicates a catabolic imbalance, a solution of butanol in water is

used. The amount of this solution ranges from 5 to 25 ml of a solution of between about 5 and 10 weight percent butanol in water. Either n-butanol or sec-butanol can be used, with n-butanol preferred for best results. It is preferable to add to the butanol solutions about 25 to 50 percent by weight (based on the amount of butanol) of coramine (niketamide) for even better results.

As with the hydrolyzed epichlorohydrin solution, these solutions are preferably administered by injection. If the type of pain cannot be characterized as acid or alkaline, then the epichlorohydrin solution should be administered. It is also possible to use mixtures of these solutions.

When the nature of the disease which is causing the pain is known, more special agents, which can treat the disease or the symptoms of the disease, can be added to these solutions. Also, the number of injections can be repeated to enhance the pain reducing effect.

The preparations of the invention have practically no toxicity in the doses used.

Treatment of symptoms of neoplastic diseases without treating the diseases themselves
US4962129

A method for treating the symptoms of a neoplastic disease without treating the disease itself which includes administering by injection an effective amount of a composition which includes the combination of two or more ketones, aldehydes, alcohols or amines having certain twin formation in a vegetable oil solution to a patient who is suffering from the symptoms of a neoplastic disease to alleviate at least some of such symptoms.

TECHNICAL FIELD

The present invention relates to compositions and methods for the treatment of symptoms of neoplastic diseases without treating the disease itself.

DETAILED DESCRIPTION OF THE INVENTION

I have found the existence of a dualism in the pathological conditions, corresponding to an anabolic-constructive or a catabolic-destructive imbalance. Symptoms and analytical data serve to recognize the type of imbalance present. Somnolence; hypothermia; constipation; polyuria; slow absorption of a skin wheel; blood eosinophilia; low serum potassium; low red cells sedimentation rates; no C reactive protein and urinary high surface tension; high pH; chloride and calcium excretion and low specific gravity characterize the anabolic imbalance. The opposite symptoms indicate a catabolic imbalance.

I found also the existence of a dualism in the activity of different agents. In general the ketones and aldehydes have an antianabolic action, while the positively charged alcohols and amines have an anticatabolic action. A method of treatment has resulted by using anabolic agents for the catabolic conditions and catabolic agents against anabolic conditions.

I have found that the presence in a molecule of a twin formation, that is, of two atoms with the same positive or negative electrical charge bound together, confers the molecule a high energetic activity. This is exerted especially upon the polar group near the twin formation.

I have found a special such activity for the molecules having two twin formations. The presence of a polar group bound to an odd numbered carbon of an aliphatic hydrocarbon having an odd number of carbons results in the presence of two twin formations. The same results have been found in aliphatic molecules having an even number of carbons with the polar group located on an even numbered carbon. The nature of the polar group determines the anabolic or catabolic character of the agent. The presence of a 3 or 5 ketone that is, of an oxygen atom bound to the carbons 3 or 5 of an aliphatic hydrocarbon having an odd number of carbons, or of a 2 or 4 ketone, where an oxygen atom is bound to the carbons 2 or 4 of an aliphatic hydrocarbon having an even number of carbons, confers to the compound a catabolic action, while a hydroxyl or amine group at the same position provides an anabolic character to the compound. The same catabolic action is found for other polar groups bound to the carbon atoms specified above, such as, for example the 3 or 5 aldehydes, and the 2 or 4 aldehydes.

Specific compounds which have been found to be useful include 3-pentanone; 3-heptanone; and 3 or 5 nonanone. These compounds, when two or more are used in combination, have provided very good action upon the symptoms of neoplastic disease without treating the diseases themselves. Propionic aldehyde in combination with a 3 or 5 ketone has also been found to be particularly effective. Combinations of 2-sec-butanone; 2-hexanone; 2 or 4 octanone; with any of the previously mentioned compounds which provide a catabolic action have been found effective. These compounds have been found effective in general for treatment of symptoms of any neoplastic diseases without treating the disease itself (i.e., whether such symptoms caused by either an anabolic or catabolic imbalance), but are even more effective for treating the symptoms caused solely by an anabolic imbalance.

Similarly, combinations of 3-pentanol; 3-heptanol; 3 or 5 nonanol; 3-penthylanone; 3-heptylanone; 3 or 5 nonylanone; 3-pentylamine; 3-heptylamine; and 3 and 5-nonylamines; 2-butanol; 2-hexanol; 2- or 4-octanol; 2-butylamine; 2-hexylamine; and 2 or 4 octylamine have a good action upon the symptoms of neoplastic diseases caused by a catabolic imbalance.

Especially favorable objective and subjective changes are found in suffering from the symptoms of neoplastic diseases without treating the diseases themselves when these compounds are administered. This indicates the important value of the combination of two agents each having the two twin formations described previously.

The use of two or more of these compounds, in combination, provides a much higher level of effectiveness for treatment of anabolic or catabolic symptoms of neoplastic diseases without treating the diseases themselves than the administration of a single agent. Preferred combinations are illustrated in the examples. The daily dosages vary according to the degree of the imbalance, but generally range from about 1/2 to 10 grams. No toxic effects have been encountered in patients which have received these compounds, even at the higher daily dosages.

All the formulations to be administered were prepared in dosages of approximately 600 mg, with the number of dosages to be taken per day depending upon the specific condition to be treated. 1 ml of a composition containing 60% of the compounds and 40% of a vegetable oil

provides 600 mg of the active ingredient. Similarly, a 70% compounds/30% vegetable oil mixture, provides 700 mg for each 1 ml dose. The dosages can range from 1 ml given once a day to 4 ml administered twice a day. Preferably, such mixtures are administered by injection.

Solutions and suspensions of these agents in oils are preferred for administration by injection. While sesame oil, tung oil, and soybean oil are preferred, any vegetable oil can be used. It is also possible to use the oil extract from the seeds of a bixa or elana plant, and the term vegetable oil is used herein to include such extracts.

It is necessary to use at least 10% vegetable oil in the formulations to avoid causing pain to the patient upon administration. Thus, the oil is primarily used as a carrier. It is important that each administered dose contain at least 600 mg (60%) of the compounds having the twin formation. Thus, the overall dosage, per day, will vary from about 0.5 to 10 grams of compounds.

Injection at the site a tumor, or at another appropriate location (such as a painful area) is the preferred method of administration. Oral administration should be avoided because the liver tends to decrease the effectiveness of the composition.

An indication of neoplastic conditions is found especially in anabolic constructive imbalances, characterized by urines with a high surface tension, high pH and low specific gravity. The clinical results are indicated by a marked action upon the different manifestations especially pain, and the presence of tumors.

Predilectly the ketones and aldehydes are used to generally treat the symptoms of any neoplastic conditions without treating the conditions themselves, even independent of the nature of the imbalance present. As such, it represents a very important, and efficient new treatment for these diseases without treating the disease themselves.

The scheme of the treatment is the following: Urine analyses are made, preferably several times a day if the condition needs stronger treatment.

As basis agents, the ketones and/or aldehyde combinations are administered by injection. When an alkaline urine is found (i.e. a pH above 7), the higher dosages of these agents can be given. For a neutral urine (pH 6-7), the alcohol compounds are administered. For acid urine (pH below 6), the amine compounds are given.

With these compositions, especially good results, both subjective and objective, were obtained in the treatment of symptoms of various neoplastic diseases without treating the diseases themselves. One or more of the symptoms which may be alleviated include pain, weakness, anemia, loss of appetite and nausea.

EXAMPLES

The scope of the invention is further described in connection with thefollowing example which is set forth for sole purpose of illustrating the preferred embodiments of the invention and which is not to be construed as limiting the scope of the invention in any manner.

The following formulations were prepared:

Example 1. Example 2.

3-Pentanone 30% 3-Pentanone 35%
3-Heptanone 30% Propionic aldehyde 35%
Sesame oil 40% Tung oil 30%

Example 3. Example 4.

3-Pentanol 30% 3-Heptylamine 30%
3-Heptanol 30% 5-Heptylamine 30%
Extract A 20% Extract B 40%

Example 5. Example 6.

2-sec-Butanone
40% 2-Octanol 33%
2-Hexanone 20% 4-Octanol 33%
Tung oil 40% Extract C 34%

Extract A is an oil extract of the seeds from a bixa plant; extract B is an oil extract of the seeds of an elana plant, while Extract C is a 50:50 mixture of Extracts A and B.

The compositions of Examples 1, 2, and 5 provide a catabolic action and thus are preferably used to treat an anabolic imbalance. Such catabolic agents can also be used to generally treat symptoms of neoplastic diseases when the type of imbalance cannot be determined. Conversely, the compositions of Examples 3, 4 and 6 provide an anabolic action, such that they are administered to patients exhibiting a catabolic imbalance.

These formulations were sterilized for injections. 2 ml injections of these compositions were given twice a day to a number of patients having various cancers, and all noted subjective improvements in the symptoms exhibited.

While it is apparent that the invention herein disclosed is well calculated to fulfill the objects above stated, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art, and it is intended that the appended claims cover all such modifications and embodiments as fall within the true spirit and scope of the present invention.

Composition and method for treatment of potassium deficiency US4649152

A method for making a composition containing a fatty acid or fatty ester compound and potassium. The compositions produced by the method. Administration of these compositions to a patient to increase the potassium content of cells or tissue having a potassium deficiency or to treat at least some of the symptoms of diseases or adverse effects caused by this potassium deficiency.

TECHNICAL FIELD

The present disclosure concerns a method to treat various conditions resulting from potassium deficiency and preparations for same.

BACKGROUND

It is known that the abnormal cells in general and the neoplastic cells in particular are poor in potassium, a fact which is considered as including and enhancing their abnormal character. It is also known that the blood plasma of subjects with such abnormal conditions is especially rich in potassium, apparently due to the body's attempt to correct the cellular potassium deficiency. The form under which the potassium is circulating in the blood, that is, mainly as ceruloplasmin, however, is not the proper form from which the potassium can be taken by the abnormal cells.

SUMMARY OF THE INVENTION

The invention comprises novel compositions of fatty acids, ester, or oils which include potassium incorporated therein. These composition are made by heating the oil component to a temperature of at least above 230 DEG C. for a sufficient time to incorporate a predetermined amount of potassium into the oil. At least about 0.1% can be used, although between 1 and 10% is preferred.

These compositions of the invention may be administered to a patient who has cells or tissue which are deficient in potassium to increase the potassium content as well as to treat the symptoms of diseases or adverse effects caused by the potassium deficient cells or tissue.

DETAILED DESCRIPTION OF THE INVENTION

I have found that in general, the abnormal cells and tissues in the body have free lipids. Thus, a lipid or compound having a lipidic character introduced into the body can be selectively taken by the abnormal cells. Accordingly, it is believed that a potassium compound having lipidic properties is useful as a therapeutic agent for patients who have such abnormal cells.

I have found that potassium can be incorporated in the molecule of a fatty acid by heating together an organic or inorganic salt of potassium with a fatty acid or its oil. Preferably, the fatty acid or oil is previously oxidized by being heated and mixed with air or oxygen. The mixtures of potassium and fatty acids or oil are heated at a temperature above about 230 DEG C. for a time until an exothermic reaction is observed, which reaction indicates that the incorporation is taking place.

Examples of the potassium/fatty acid or oil compositions that can be used according to the invention include the reaction products of allylic unsaturated fatty acids or esters and a potassium salt. These reaction products are produced by heating a liquid composition containing a fatty acid or fatty ester, structurally characterized by allylic unsaturation with a potassium salt. Applicant believes that any potassium salt may be used in this invention. Preferably, the potassium salt is an organic potassium salt such as potassium acetate or potassium carbonate, and the liquid is preferably oxidized for example, by bubbling air or oxygen through the reaction mixture.

The allylically unsaturated compound is preferably a naturally occurring oil containing

polyunsaturated fatty esters, such as an animal, vegetable, or fish oil, and, particularly, polyunsaturated vegetable oils. Sesame oil, a vegetable oil consisting largely of triglycerides, is the most advantageous composition found to date in the practice of this invention.

The composition utilized should contain a significant percentage of molecular species having allylic moieties to render the compositions useful according to the invention. Such moieties are indicated by the following partial structures --CH.dbd.CH--CH2 --CH.dbd.CH-- and/or --CH.dbd.CH--CH.dbd.CH--CH2 --. As indicated, the unsaturation can be conjugated or nonconjugated, but the composition must contain allylic methylene hydrogen.

Such compositions may initially be oxidized or heated in the presence of air or oxygen at the temperature range between about 100 DEG C. and about 150 DEG C. The oxygen can be obtained by merely heating the composition in a vessel which is open to the atmosphere, but preferably and advantageously, the source of oxygen is a gas such as air which is injected into the heated oil. Introduction of air also provides a source of agitation.

The heating step is conducted for a period of from about 15 minutes to about two hours. The temperature should be maintained at an upper limit within the range of about 230 DEG C. to 250 DEG C., and preferably about 235 DEG C. to 240 DEG C. These temperature limitations are based on a heating time of about one-half hour. The temperatures can be altered within limits depending on the time of heating. For example, when the temperature is about 235 DEG C., the time is about one-half hour, while temperatures as high as 250 DEG C. require a shorter period of time for heating. Higher temperatures for a prolonged period of time tend to degrade the composition and should thus be avoided.

Agitation, by stirring for example, aids in the reaction, and experiments to date indicate that a fairly violent stirring is advantageous. The introduction of air into the mixture during the heating is also very advantageous, particularly when the mixture is not subjected to prolonged heating and thus, is the preferred method. The mixing or stirring can be accomplished with the introduction of the air.

After the reaction has taken place, the mixture is cooled. The remaining fluid is ready for use after appropriate sterilization for injection or incorporated into capsules, such as gelatin, for oral administration.

The precise nature of the compositions which result from the above-described treatment or the identity of the effective component or components is not presently known. It is known, however, that these compositions do include potassium and that a proportion of potassium in the range of about 1 to 10 weight percent has been found to be effective.

As mentioned above, although any potassium salt may be used, an organic salt of potassium, such as potassium carbonate or potassium acetate, is preferred, with the potassium bonding the eleostearic acid present in this oil. Although any amount above 0.1% of potassium incorporated into the composition is useful, the preferred amount ranges between about 1 to 10 weight percent.

The products obtained have the potassium incorporated in general at the level of the double bonds of the different unsaturated fatty acids, this causes their toxicity to be exceptionally low. The injection of 1 ml of a product having 5% potassium to a mouse does not kill it.

The incorporated potassium composition may be administered orally, by injections, sublingually or rectally in the appropriate formulation.

The incorporated potassium is believed to be absorbed by the abnormal cells, thus compensating for their low potassium content. This treatment produces objective and subjective improvement in the conditions, of patients having a variety of diseases based upon such abnormal cells. The neoplastic diseases are examples of diseased in which low cellular potassium abnormal cells are found.

Such low cellular potassium abnormal cells are believed to cause an catabolic imbalance in the body. This catabolic imbalance can be analyzed and diagnosed by blood and urine analyses. A low eosinophilia (below 100/cmm), a high red cell sedimentation rate (above 15 ml/1 hour), a high serum potassium (above 4.5 mEq), a urinary acid pH (below 7), high specific gravity (above 1.016), low surface tension (below 89 dynes/cm), and low calcium or chloride excretion are indications of an catabolic imbalance. (The opposite analyses would indicate a anabolic imbalance.)

These analyses and clinical manifestations have to be changed by the administration of the incorporated potassium compound. In a 5% potassium incorporated preparation, amounts from about 1/10 to 2 ml daily are predilectly used for the treatment of this catabolic imbalance. For other conditions with anabolic imbalances, doses from about 2 to 10 ml daily are predilectly used. In general the higher the dose used, the better are the clinical results.

Interesting results are those concerning pain, the changes induced in the lesions manifesting first an action upon pain. Manifest changes in the tumors and in the subjective manifestations of the neoplastic diseases are obtained even in a very short time. Thus, the incorporated potassium appears as a predilect treatment of the symptoms of neoplastic conditions, and possibly to the treatment of such condition themselves.

Good results were also obtained in the use of the incorporated potassium compounds for the different manifestations of AIDS (acquired immune deficiency syndrome) as well as for the ARC (AIDS related complex).

Interesting also are the results in almost all the different conditions, such as neurological conditions, epilepsy and others, the problem of cellular potassium deficiency being a general pathological occurrence. Interesting is the action of the lipidic potassium products on the viral infections.

The incorporated potassium composition may be administered together with different other agents.

Composition and method for treatment of copper deficiency US4677118

A method for making a composition containing a fatty acid or fatty ester compound and copper. The compositions produced by the method. Administration of these compositions to a patient to increase the copper content of cells or tissue having a copper deficiency or to treat at least some of the symptoms of diseases or adverse effects caused by this copper deficiency.

TECHNICAL FIELD

The present disclosure concerns a method to treat various conditions resulting from copper deficiency and preparations for same.

BACKGROUND

It is known that the abnormal cells in general and the neoplastic cells in particular are poor in copper, a fact which is considered as including and enhancing their abnormal character. It is also known that the blood plasma of subjects with such abnormal conditions is especially rich in copper, apparently due to the body's attempt to correct the cellular copper deficiency. The form under which the copper is circulating in the blood, that is, mainly as ceruloplasmin, however, is not the proper form from which the copper can be taken by the abnormal cells.

SUMMARY OF THE INVENTION

The invention comprises novel compositions of fatty acids, ester, or oils which include copper incorporated therein. These composition are made by heating the oil component to a temperature of at least above 230 DEG C. for a sufficient time to incorporate a predetermined amount of copper into the oil. At least about 0.1% can be used, although between 1 and 10% is preferred.

These compositions of the invention may be administered to a patient who has cells or tissue which are deficient in copper to increase tthe copper content as well as to treat the symptoms of diseases or adverse effects caused by the copper deficient cells or tissue.

DETAILED DESCRIPTION OF THE INVENTION

I have found that in general, the abnormal cells and tissues in the body have free lipids. Thus, a lipid or compound having a lipidic character introduced into the body can be selectively taken by the abnormal cells. Accordingly, it is believed that a copper compound having lipidic properties is useful as a therapeutic agent for patients who have such abnormal cells.

I have found that copper can be incorporated in the molecule of a fatty acid by heating together an organic or inorganic salt of copper with a fatty acid or its oil. Preferably, the fatty acid or oil is previously oxidized by being heated and mixed with air of oxygen. The mixtures of copper and fatty acids or oil are heated at a temperature above about 230 DEG C. for a time until an exothermic reaction is observed, which reaction indicates that the incorporation is taking place.

Examples of the copper/fatty acid or oil compositions that can be used according to the invention include the reaction products of allylic unsaturated fatty acids or esters and a copper salt. These reaction products are produced by heating a liquid composition containing a fatty acid or fatty ester, structurally characterized by allylic unsaturation with a copper salt. Applicant believes that any copper salt is suitable for this invention. Preferably, the copper salt is an organic copper salt such as cupric acetate, and the liquid is preferably oxidized for example, by bubbling air or oxygen through the reaction mixture.

The allylically unsaturated compound is preferably a naturally occurring oil containing

polyunsturated fatty esters, such as an animal, vegetable, or fish oil, and, particularly, polyunsaturated vegetable oils. Sesame oil, a vegetable oil consisting largely of triglycerides, is the most advantageous composition found to date in the practice of this invention.

The composition utilized should contain a significant percentage of molecular species having allylic moieties to render the compositions useful according to the invention. Such moieties are indicated by the following partial structures --CH.dbd.CH--CH2 --CH.dbd.CH-- and/or --CH.dbd.CH--CH.dbd.CH--CH2 --. As indicated, the unsaturation can be conjugated or nonconjugated, but the composition must contain allylic methylene hydrogen.

Such compositions may initially be oxidized or heated in the presence of air or oxygen at the temperature range between about 100 DEG C. and about 150 DEG C. The oxygen can be obtained by merely heating the composition in a vessel which is open to the atmosphere, but preferably and advantageously, the source of oxygen is a gas such as air which is injected into the heated oil. Introduction of air also provides a source of agitation.

The heating step is conducted for a period of from about 15 minutes to about two hours. The temperature should be maintained at an upper limit within the range of about 230 DEG C. to 250 DEG C., and preferably about 235 DEG C. to 240 DEG C. These temperature limitations are based on a heating time of about one-half hour. The temperatures can be altered within limits depending on the time of heating For example, when the temperature is about 235 DEG C., the time is about one-half hour, while temperatures as high as 250 DEG C. require a shorter period of time for heating. Higher temperatures for a prolonged period of time tend to degrade the composition and should thus be avoided.

Agitation, by stirring for example, aids in the reaction, and experiments to date indicate that a fairly violent stirring is advantageous. The introduction of air into the mixture during the heating is also very advantageous, particularly when the mixture is not subjected to prolonged heating and thus, is the preferred method. The mixing or stirring can be accomplished with the introduction of the air.

After the reaction has taken place, the mixture is cooled. The remaining fluid is ready for use after appropriate sterilization for injection or incorporated into capsules, such as gelatin, for oral administration.

The precise nature of the compositions which result from the above-described treatment or the identity of the effective component or components is not presently known. It is known, however, that these compositions do include copper and that a proportion of copper in the range of about 1 to 10 weight percent has been found to be effective.

As mentioned above, although any copper salt may be used, an organic salt of copper, such as cupric acetate, is preferred, with the copper bonding the eleostearic acid present in this oil. Although any amount above 0.1% of copper incorporated into the composition is useful, the preferred amount ranges between about 1 to 10 weight percent.

The products obtained have the copper incorporated in general at the level of the double bonds of the different unsaturated fatty acids, this causes their toxicity to be exceptionally low. The injection of 1 ml of a product having 5% copper to a mouse does not kill it.

The incorporated copper composition may be administered orally, by injections, sublingually

or rectally in the appropriate formulation.

The incorporated copper is believed to be absorbed by the abnormal cells, thus compensating for their low copper content. This treatment produces objective and subjective improvement in the conditions, of patients having a variety of diseases based upon such abnormal cells. The neoplastic diseases are examples of diseased in which low cellular copper abnormal cells are found.

Such low cellular copper abnormal cells are believed to cause an anabolic imbalance in the body. This anabolic imbalance can be analyzed and diagnosed by blood and urine analyses. An eosinophilia (above 100/cmm), a low red cell sedimentation rate (below 15 ml/1 hour), a low serum potassium (below 4.5 mEq), a urinary alkaline pH (above 7), low specific gravity (below 1.016), high surface tension (above 89 dynes/cm), and high calcium or chloride excretion are indications of an anabolic imbalance. (The opposite analyses would indicate a catabolic imbalance.)

These analyses and clinical manifestations have to be changed by the administration of the incorporated copper compound. In a 5% copper incorporated preparation, amounts from about 2 to 10 ml daily are predilectly used for the treatment of this anabolic imbalance. For the neoplastic conditions wwith catabolic imbalances, low doses from 1/10 to 2 ml daily are predilectly used. In general the higher the dose used, the better are the clinical results.

Interesting results are those concerning pain, the changes induced in the lesions manifesting first an action upon pain. Manifest changes in the tumors and in the subjective manifestations of the neoplastic diseases are obtained even in a very short time. Thus, the incorporated copper appears as a predilect treatment of the symptoms of neoplastic conditions, and possibly to the treatment of such condition themselves.

Good results were also obtained in the use of the incorporated copper compounds for the different manifestations of AIDS (acquired immune deficiency syndrome) as well as for thee ARC (AIDS related complex).

Interesting also are the results in almost all the different conditions, such as neurological conditions, epilepsy and others, the problem of cellular copper deficiency being a general pathological occurrence. Interesting is the action of the lipidic copper products on the viral infections.

The incorporated copper composition may be administered together with different other agents.

Treatment of symptoms of neoplastic diseases with nucleoproteins US4701442

A method for making a composition containing a fatty acid or fatty ester compound and copper. The compositions produced by the method. Administration of these compositions to a patient to increase the copper content of cells or tissue having a copper deficiency or to treat at least some of the symptoms of diseases or adverse effects caused by this copper deficiency.

TECHNICAL FIELD

The present invention is related to compositions and methods for the treatment of symptoms of different neoplastic diseases.

BACKGROUND OF THE INVENTION

The histones are body constituents which are presently considered to be of secondary importance in the protection of the body's nucleic acids.

I found that the histones are playing a capital role in biology. The body hierarchic organization is made up of successive entities at various levels. Each basic entity comprises an electropositive principal part bonded to an electropositive secondary part. The principal part remains unchanged, protected by the secondary parts through its adequate changes.

I found the histones to be formed by a series of histosomes, round formations bonded consecutively in a sequence. Each histosome is surrounded by its self-manufactured nucleoproteic material. The histosomes and the nucleoproteic material together form the nucleosomes. The nucleosomes bonded in a row make up the genes. The electropositive histones represent the principal part, with the electronegative nucleoprotein as the secondary part bonded thereto. Together they form the next level in the hierarchy, the genes.

The nucleoproteic material as the active part of the gene is manufactured by the histones as principal part. As the secondary constituent, the nucleoproteic material has the capacity to change. Due to this capacity, nucleoproteic material may be changed through proper external intervention.

Any abnormal body condition corresponds to abnormal nucleoproteic materials, usually with also abnormal histosomes forming together abnormal nucleosomes.

Chronic abnormal conditions, such as neoplastic conditions, can result from the intervention of specific abnormal histones. I have found the histones in general and from the neoplastic material in special to have a specific capacity to possess carcinogenic properties. The histones from the neoplastic material have a specific capacity to possess carcinogenic properties. The repeated injections of these histones into mice have induced the appearance of different tumors at the site of the injections as well as in other parts of the body.

The abnormal conditions which result from the presence of abnormal histones and nucleoproteins give rise to a foreign formation known as isoparasite. The abnormal neoplastic cells are essentially a parasite on the host tissue.

Because of the nucleoproteic material's ability to change, it may be changed by injecting the proper substance. The administration of foreign nucleoproteic material may act as antiabnormal nucleic material and indirectly as antiabnormal histones. The presence of an abnormal entity in a body with its own foreign nucleoproteic material enables this nucleoproteic material to be changed when a new nucleoproteic material is introduced into the body. This has led to the use of such foreign nucleoproteic materials in order to the change the abnormal nucleoproteic material present in lesions.

SUMMARY OF THE INVENTION

The invention relates to a process for preparing nucleoproteic material which comprises immersing organic materials into a suitable solvent for a sufficient time to extract the nucleoproteins from these materials, adding a sufficient amount of an acid to form a precipitate of nucleoproteic material, and recovering said nucleoproteic material precipitate. This precipitate may be washed with distilled water and separated again by centrifugation or filtration.

In this process, a preferred solvent system is water which is slightly alkaline. The material used as a source of nucleoproteins is an organic material, especially full animals or their organs, including at least liver, spleen, intestines, thymus or testes. Microbes, fungi or plants may also be used to obtain nucleoproteins.

Also, the solvent may further comprise an alkaline component, such that the solvent system has a pH between about 7 and 8. The solvent can be heated to boiling to increase the extraction of the desired material. A preferred acid for precipitating nucleoproteins is acetic acid. The resulting precipitate can be recovered by filtration or centrifugation.

Another aspect of the invention relates to compositions of nucleoproteic material produced according to the above-described process.

Preferably, an effective formulation comprises water or alkaline containing about 5-50% of the nucleoproteic composition in suspension. The pH of the formulation may be adjusted with the addition of an alkaline material to a pH range of preferably between 5.5 and 6.5.

The invention also contemplates a method for alleviating symptoms of neoplastic diseases which comprises preparing a formulation comprising an effective amount of the nucleoprotein precipitate, sterilizing this formulation, and administering the formulation to a patient having symptoms of a neoplastic disease. The symptoms of the neoplastic diseases to be alleviated include at least one of pain, anemia, weakness, loss of appetite, nausea and the presence of characteristic abnormal cells and lesions. These formulations are preferably administered by intramuscular injections.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Foreign nucleoproteic material is obtained from a chosen material through extraction by cold, or preferably, by boiling water. The water should preferably be slightly alkaline. This water solution may be then acidified by adding acetic acid or other acids. A precipitate results, which is then separated by centrifugation or filtration. If necessary, this precipitate is treated with sodium hydroxide (NaOH) or another alkaline agent to reach a desired pH of between approximately 5.0 and 6.5. An adequate portion of the product is suspended in water, saline, or other injectable media. The so obtained product is then sterilized for injections. This material is equivalent to nucleoproteins or nucleoproteins which partially may be in the form of salts or esters. Nucleoproteins of any biological material may thus be obtained, each product having a specific capacity to effectively act on a specific pathogenic condition.

An observation of the in vitro (experimentally induced biological processes outside the organism) action upon the cultures of cells, especially the neoplastic cells, will lead to a determination of the most active agents. An observation of in vivo (experimentally induced biological processes in the organism) action upon specific abnormal conditions, especially neoplastic conditions or diseases, is the last means of determining the effectiveness of

specific agents upon specific pathological conditions. Neoplastic diseases is used to mean cancers, sarcomas, leukemias, etc.

The nucleoprotein compounds obtained from the entire body or from organs such as the thymus, intestines, liver, spleen and testes of various animals have revealed interesting results against various symptoms. In an attempt to use more specific agents, nucleoprotein compounds obtained from the organs directly involved in the pathological condition are employed. The same may be said for the neutralizing agent if used in obtaining the respective salts or esters of these materials.

A preferred material, carp, is used to provide the nucleoproteins because it is known for its longevity, thus indicating a special ability to resist disease. The thymus, spleen and intestines, in particular, have this special defense capacity. Nucleoproteins obtained from the thymus, spleen, or intestines of carp have resulted in effective action upon different conditions. In general, suspensions from 5% to 50%, preferably approximately 35%, in water or saline are used. This concentration has been determined through experimental and clinical applications in a large variety of acute and chronic abnormal conditions. These conditions include pain, anemia, weakness, loss of appetite and lesions of a neoplastic nature. Good objective and subjective results were obtained in treating neoplastic diseases, such as cancers, sarcomas and leukemia, even after a short treatment by the use of preparations from carp intestines. Pig organs, such as the intestines, are another preferred source of such nucleoproteins.

Especially interesting is the use of the nucleoproteins obtained from microbes, fungi or plants in the treatment of neoplastic conditions in accordance with this invention.

An entire series of pathological conditions has responded within a short time of the administration of different preparations of the invention.

In all cases of cancer treated with these preparations, effects on the existing lesions were objectively and subjectively very favorable. In most of the cases, there was a decrease in pain and the other associated symptoms following the injections. In a few cases, favorable local effects were obtained with only one injection. The changes in the lesions that took place within a short time are indicative of the effective action of these agents upon the lesions themselves.

Alternatively, the precipitated nucleoproteins themselves may be used, instead of their salts or esters. Another alternative that may be utilized is the product obtained by the water extraction, as the material directly extracted through boiling.

The fact that almost all of the subjective and objective results obtained in the different cases of cancer treated were favorable indicates the value of this specific approach in the fight against this disease.

The basic concept of the pathogenic role of specific histones and nucleic material, with the consequent therapeutic use of specific nucleoprotein compounds, is opening an entirely new field in the treatment of general abnormal conditions and specifically in the treatment of various neoplastic conditions.

EXAMPLES

The scope of the invention is further described in connection with the following examples which are set forth for the sole purpose of illustrating the preferred embodiments of the invention and which are not to be construed as limiting the scope of the invention in any manner. In these examples, all parts given are by weight unless otherwise specified.

EXAMPLE 1

W. M., 27 years old, had lymphatic leukemia for years. At the start of the treatment, the blood count showed 186,000 leukocytes. The patient was treated with injections of 3 cc daily of a preparation of 20% of the nucleoproteins of pig intestines. Blood analyses taken every 10 days from the start of the injection showed the following changes in leukocytes: 130,000, 40,000, 12,000, 10,000, and 3,500 leukocytes per cmm. The general condition of the patient progressively became better.

EXAMPLE 2

R. E., 34 years old, had cancer of the stomach, and felt severe pain after eating. The patient was very weak and practically unable to walk. After a week of treatment with 2 daily injections of 2 cc of a preparation of 20% pig intestine nucleoproteins, the patient has been able to walk 9 blocks and eat meat totally without pain.

EXAMPLE 3

Mrs. E. S., 78 years old, had cancer of the breast with a metastases of 5/5 cm on the right clavicule. After 10 days of treatment with a preparation of 1 cc of 20% of the nucleoproteins of pig intestines twice daily, the lesion could no longer be located.

EXAMPLE 4

J. R., 53 years old, with jaundice, cohexia and pain from massive liver metastases, has had pain relieved and strength improved after the injection of 3 cc of a suspension of 20% of pig intestine nucleoproteins, twice daily for one week.

EXAMPLE 5

L. W., 53 years old with very painful left side rib metastases, has had the pain totally controlled after 2 injections of 3 cc of a preparation of a mixture of equal amounts of the nucleoproteins from pig intestines and carp, the mixture totalling a suspension of 20%.

EXAMPLE 6

W. P., had cancer of the esophagus and manifest difficulties in eating. With a teatment of 2 cc daily of a 30% suspension of pig intestines nucleoproteins for one week, all the symptoms have disappeared, and the patient resumed eating normally.

The disappearance of pain, with a general well being sensation was observed in many additional patients, each having different neoplastic conditions, following in general by only a few injections of different nucleoprotein preparations in accordance with the invention and the preceding examples.

Method for terminating pregnancy
US4609552

A method for terminating pregnancy which comprises internally administering to the body a sufficient amount of a bivalent negative sulfur composition to induce menstruation.

TECHNICAL FIELD

This invention relates to a method for terminating pregnancy by administering to the body an amount of elemental sulfur or a non-toxic bivalent negative sulfur composition sufficient to terminate the pregnancy by inducing menstruation.

DETAILED DESCRIPTION OF THE INVENTION

Examples of non-toxic bivalent negative sulfur compositions that can be used according to the invention include the reaction products of allylic unsaturated fatty acids or esters and sulfur. As disclosed in U.S. Pat. No. 4,368,206, such reaction products are produced by oxidizing a liquid composition containing a fatty acid or fatty ester, structurally characterized by allylic unsaturation, for example, by bubbling air through the reaction mixture. The fatty acid or ester advantageously includes elemental sulfur and/or a conventional free radical initiator such as tertiary-butyl peroxide during the heating step.

The allylically unsaturated compound is preferably a naturally occurring oil containing polyunsatuarated fatty esters, such as an animal, vegetable, or fish oil, and, particularly, polyunsaturated vegetable oils. Sesame oil, a vegetable oil consisting largely of triglycerides, is the most advantageous composition found to date in the practice of this invention.

The composition utilized should contain a significant percentage of molecular species having allylic moieties to render the compositions useful according to the invention. Such moieties are indicated by the following partial structures --CH.dbd.CH--CH2 --CH.dbd.CH--and/or --CH.dbd.CH--CH.dbd.CH--CH2. As indicated, the unsaturation can be conjugated or nonconjugated, but the composition must contain allylic methylene hydrogen.

Such compositions should be oxidized or heated in the presence of oxygen at a temperature range between about 110 DEG C. and about 150 DEG C. The oxygen can be obtained by merely heating the composition in a vessel which is open to the atmosphere, but preferably and advantageously, the source of oxygen is a gas such as air which is injected into the heated oil. Introduction of air also provides a source of agitation.

As previously stated, it is most advantageous to add elemental sulfur such as sublimed, precipitated, or washed sulfur to the compositions so that the sulfur is present with oxygen during at least a portion of the heating period and the sulfur becomes incorporated into the composition. Additionally, a previous batch of the oxidized oil with or without sulfur or any commonly known and available free radical initiator, such as terbutyl peroxide, may advantageously be present during at least a portion of the heating period.

If sulfur is added to the selected composition, for example, sesame oil, the temperature should be maintained at an upper limit within the range of about 120 DEG C. to about 130

DEG C., and preferably about 125 DEG C. to 127 DEG C. These temperature limitations are based on a heating time of about one-half hour. The temperatures can be altered within limits depending on the time of heating. For example, the temperature can be 129 DEG-130 DEG C. if the time is shorter, or at temperatures as high as 150 DEG C. for brief periods of time. High temperatures for a prolonged period of time tend to degrade the composition and should thus be avoided.

If sulfur is not present during the heating period, the temperature should be maintained in the range between about 110 DEG C. and about 150 DEG C. and preferably in the range between about 120 DEG C. and about 140 DEG C.

The heat treatment is conducted for a period of from about 15 minutes to about two hours. If sulfur is present, optimal results are obtained if the heat treatment is conducted for a period of time between about 30 minutes and about 1 hour. If a free radical initiator is present, or if a selected composition inherently contains a significant amount of initiator, the heat treatment period may be conducted for a much shorter period of time.

The precise nature of the compositions which result from the above-described treatment or the identity of the effective component or components is not presently known. Also, it appears that a correlation exists between a composition useful for the purpose of the invnetion and its presumed perioxide or hydroperoxide content. By adhering to the process according to this invention, it has been found that efficacious compositions are produced which yield a significant peroxide titer when monitored by conventional iodometric analysis, the results being expressed for example, in terms of microequivalents per gram or milliequivalents per kilogram. By significant peroxide titer is meant a value obtained which is greater than that which inherently may be present in the initial untreated compound.

In the case of triglycerides which contain the allylic type unsaturation as described above, the resulting oxidized species is thought to be a hydroperoxide represented by the following partial structure ##STR1## as interpreted via UV spectroscopic analysis, inter alia.

Whatever the nature of the oxidized species (with or without the addition of sulfur), it appears amenable to monitoring by conventional iodometric analysis.

Although it appears that the activity of the composition is coincident with the presence of perioxides or hydroperoxides, the efficacious agent need not necessarily be directly derived from these classes. It may be in fact be those species derived from radicals resulting from decomposition of compounds of this class and may involve reaction with other molecules of, for example, triglyceride oils or sulfur including olefinic polymerization products and/or lower molecular weight decomposition products of the oils or additional products with sulfur such as sulfides, disulfides, hydropersulfides, etc.

With regard to a preferred embodiment, it appears that the presence of elemental sulfur (approximately 1% by weight based on sesame seed oil) during the oxidation of sesame seed oil acts to increase the amounts of oxidation products (conjugated hydroperoxides, diene, triene, unsaturated carbonyl) and that this increase appears optimal near 127 DEG C. as evidenced by UV spectroscopic analysis studies. In the absence of sulfur, it appears that the region near 137 DEG C. is optimal for the production of oxidation products.

As mentioned above, it appears that the most effective compositions are those which have a

relatively high peroxide titer. Such trend of effectiveness agrees in general with the results of a peroxide analysis involving the above-identified oils in their untreated state and when oxidized in the presence of elemental sulfur under similar conditions as shown in Table I.

It is believed that the lower peroxide titer of cottonseed oil is due to the presence of natural antioxidants. The elimination of the anti-oxidants from oils such as corn and cottonseed oil or the use of the relatively pure allylically unsaturated compounds or mixtures thereof will result in a substantially increased peroxide titer when treated according to this invention.

TABLE I
PEROXIDE ANALYSIS (meq/kg)

Oil Used	"A" Oil Treated*	"B" .DELTA. = "B - A" (Peroxide Oil Saturated With Sulfur Difference In Analysis) With Sulfur and Air Peroxide
Sesame Seed	18.8	35.7 (10.2) 16.9
Corn	11.3	14.9 (6.8) 3.6
Cottonseed	10.9	10.2 (7.3) -0.7**
Olive	12.4	13.8 (5.9) 1.4
Triolein	8.6	8.5 (7.2) -0.1**

*Heated at 127 DEG C. for 0.5 hrs with 90 1/min air addition and rapid mechanical stirring and containing 1.0% elemental sulfur by weight.
**Within experimental error.

Triolein contains only oleic acid moieties which are characterized by the allylically unsaturated group --CH.dbd.CH--CH2 --and hence is quite difficult to oxidize, * particularly when compared to the preferred sesame seed oil or other polyunsaturated oils. A peroxide titer value of 35.7 meq/kg has been attained for the sesame seed oil-sulfur-oxygen treated composition whle sesame seed oil oxidized alone at 137 DEG C. yields a value of 63.3 meq/kg.

J. Sci. Fd. Agric. 1975, 26, 1353-1356. A peroxide titer value of 35.7 meq/kg [.DELTA.= (35.7-18.8)=16.9] has been attained for the sesame seed oil-sulfur-oxygen treated composition while sesame seed oil without sulfur oxidized at 137 DEG C. yields a value of 63.3 meq/kg [.DELTA.=(63.3-10.2)=53.1].

Generally a substantial increase in the peroxide titer value can be defined as .DELTA.3 to about .DELTA.100 in cases where sulfur is incorporated into the composition and as from about .DELTA.3 to about .DELTA.400 when the oil is oxidized alone, or in the absence of sulfur.

The process used for determining the peroxide titer values discussed and reported herein are determined by placing a 2 gram sample of the composition in a flask purged with nitrogen, and adding thereto 2 ml of concentrated acetic acid and 0.5 grams of potassium iodide. The mixture is capped to exclude air and allowed to remain in the dark for 30 minutes to complete the reaction. The side walls are then wet with a minimum amount of water and approximately 1-2 ml of a 2% starch added thereto. The solution is then immediately titrated to the end point with 0.007 normal Na2 S2 O3 solution. The end point is white when small amounts of peroxides are present and slightly yellow when larger amounts are present.

The compositions as prepared according to the process of this invention should be used relatively soon after preparation as there is indication that the peroxide titer values and effectiveness of the compositions decrease upon aging.

Preferred compositions according to this invention can be prepared by adding the sulfur to the oil, such as sesame oil, and heating the mixture with agitation at a temperatures of about 130 DEG C. For clear solutions, the mixture can be heated between about 120 DEG C. and 127 DEG C. Heating the mixture above about 130 DEG C. for a sufficient time causes a progressive color change in the mixture which otherwise does not appear to be detrimental. The temperatures given above relate to the use of sulfur with sesame oil. Ranges of temperatures which can be used to produce the compositions made according to this invention may vary with the particular oil being used, but generally temperatures between about 120 DEG C. and 150 DEG C. are sufficient for most oils when sulfur is added.

It is preferred to heat the oil and sulfur at about 150 DEG C. for 15 minutes to a half hour or until the compositions turn to a fairly deep black color. The oil used, together with sublimed or precipitated sulfur, is preferably rich in conjugated and polyunsaturated acids, such as safflower, corn, cod liver, sardine, salmon or tung oil or an oil extract from Bixa orellana seeds. The polunsaturated fatty acids can be treated with 50% KOH before incorporation of the sulfur therein. The oils having the sulfur incorporated therein and the crystals which are separated therefrom after cooling can be administered separately but preferably together. These compositions heated to about 150 DEG C. are presently preferable.

If the oil and sulfur is heated below about 90 DEG C., it is difficult to incorporate the sulfur into the oil by heating and stirring alone. The best results have been obtained to date by maintaining the temperature used in forming the compositions over a prolonged period of time from about 30 minutes to one hour. Stirring aids in the reaction, and experiments to date indicate that a fairly violent stirring is advantageous. The introduction of air into the mixture during the heating is also very advantageous, particularly when the mixture is not subjected to prolonged heating and thus, is the preferred method. The mixing or stirring can be accomplished with the introduction of the air.

After the reaction has taken place, the mixture is cooled. The remaining fluid is ready for use after appropriate sterilization for injection or incorporated into capsules, such as gelatin, for oral administration. As mentioned above the sulfur crystals remaining in the bottom of the reaction vessel may also be used with or without the oil.

The amount of sulfur incorporated into the oil is advantageously between about 0.1% to 2.5% by weight, based on the oil. If higher amounts of sulfur are used, it will generally precipitate. There appears to be no advantage to using higher amounts of sulfur in any event since the ultimate dosage given to the patient is the criterion, rather than the amount of sulfur content

in the oil.

As can be observed from Example 2 below, the incorporation of the sulfur into the oil also seems to be limited to about 1% by the process presently described and utilized for producing these sulfurized unsaturated oils.

The sulfur content can be much less than about 1% if desired and smaller sulfur content is advantageous when administered by injection. Varying the amount of sulfur below about 1% incorporated in the polyunsaturated oils for oral administration only affects the number of capsules to be taken at a given time by a particular patient.

Experiments to date indicate that the optimum sulfur content for oral administrations is about 1% and by injection about 0.1% to 0.3% by weight of the sulfur based on the weight of the oil.

Further examples of non-toxic bivalent negative sulfur compounds that can be used include thiosulfates, thiosinamine, thio or thiol compounds, such as thioacids and their non-toxic salts or esters, thioglycerol, thioglycol, thiopropanediol, dithiopropanol, ethyl sulfide and ethylene sulfide. Colloidal sulfur can also be used. Colloidal sulfur has been found to form sulfides in the intestines.

The invention also includes the use of selenium in place of elemental sulfur and for the same use. When using selenium it is combined with the allylic moiety in the same manner as sulfur but heated to a temperature in the range of 230 DEG to 250 DEG C., preferably about 240 DEG C. from 15 minutes to an hour or more until the peroxide titer value is substantially greater than that of the untreated allylic moiety in the same manner as disclosed herein with respect to the use of sulfur. These compositions into which selenium is incorporated have to date not indicated as good an effect as those compositions into which sulfur is incorporated.

The amount of bivalent negative sulfur compound that is administered to terminate the pregnancy by including a menstruation period will, of course, vary depending upon the particular compound being employed, since the activity of the sulfur and percentage found therein will be somewhat variable. The body weight is also a factor as is well known in the art. Generally, for the average size human, a dose of about 1 gram 3 to 5 times a day is sufficient to terminate the pregnancy by inducing menstruation. Therapy can be continued from day to day until menstruation reappears. Usually this occurs within 1 to 2 days of treatment.

The inducement of the menstruation and the corresponding termination of the pregnancy is effected by a catabolic local process, with a lytic action upon the uterine mucuous membrane. The administration of these compounds causes predirectly uterine catabolic changes which restores the menstruation.

The invention is useful for the treatment of lower animals as well as humans.

The compositions are preferably administered orally, but can be administered by injection, as suppositories or even vaginally.

An advantageous oral dose has been found to be about 20 drops in a gelatine capsule. Patients are generally advised to take one capsule twice a day, for two days after which menstruation

should begin.

When the sulfurized oil is used by injection, such as intramuscularly or intraperitoneally, it is advantageous to have the sulfur contained in the sulfurized oil below about 0.5% by weight, preferably between about 0.1% to 0.3% by weight, and to inject for 1/2 to 3 ml of this solution into the patient. Experiments to date indicate that the injection of sulfurized oil is somewhat painful when it contains above about 0.5% sulfur. Administration by injection is, of course, not necessary but it may act faster initially. Generally if a person is given the initial injection of the sulfurized oil, he can also be given a supply of the oral capsules and directed to take 3 to 4 capsules a day following the injection for one week.

EXAMPLE 1

A sulfurized oil was prepared by mixing 50 grams of sublimed sulfur, obtained from Fisher Scientific, with one liter of sesame oil. The mixture was heated under fairly rapid agitation by air to a temperature of about 127 DEG C. until all of the sulfur was incorporated into the sesame oil. The reaction mixture was then cooled to room temperature, producing at the bottom of the reaction vessel a small amount of sulfur crystals. The crystals were then separated from the liquid by filtration and about half of the crystals replaced in the resulting liquid, wherein they slowly dissolved.

The resulting sulfurized oil was then incorporated into gelatin capsules in the amount of (about 20 drops) per capsule.

EXAMPLE 2

For women of average size, these recommended dosage of such capsules is one capsules, twice a day for 2 days, and this has been found sufficient in most cases to induce menstruation and terminate the pregnancy. One skilled in the art would be able to vary the dosage according to the size of the person to be treated; 4 g. of sulfur were weighed out and placed in an Erlenmeyer flask. 200 ml of sesame oil were added; the contents were heated to 125 DEG C. with stirring until the sulfur dissolved. The flask was removed from heat and allowed to cool to room temperature (5 hours). Sulfur crystals were filtered into a Buchner funnel, washed thoroughly with hexane to remove residual oil, and weighed.

The above example was repeated three times. The washed sulfur precipitate was weighed in each trial and the amount of sulfur in the sesame oil calculated by difference as follows:
Initial weight of sulfur: 4.00 g
Weight of sulfur ppt.:
Trial 1 2.05 g
Trial 2 2.00 g
Trial 3 1.92 g
% (w/v) sulfur in sesame oil:
Trial 1 1.02%
Trial 2 1.00%
Trial 3 0.96%
Average 0.99%

From this it was concluded that the solutions contained approximately 1% sulfur after filtration. These formulations were substituted into the capsules of Example 1 and were found

to produce similar results.

Method for counteracting the adverse effects of sodium chloride US4663165

A composition comprising at least one compound containing a cation of magnesium, calcium, or strontium and an anion of bivalent negative sulfur or selenium, and at least one compound containing a cation of lithium or potassium and an anion of bivalent negative sulfur or selenium. Also, a composition comprising salt and the previously described compounds along with a method for counteracting the adverse effects of sodium chloride on a human body by administering to the body between about 0.5 and 10% of one of the disclosed compositions, preferably in a water solution.

TECHNICAL FIELD

This invention relates to new and useful improvements in a method for counteracting the deleterious effects of sodium chloride on the human body. More particularly, the invention relates to the administration of specific compositions or mixtures of compounds which are antagonists for sodium chloride.

BACKGROUND ART

It has become apparent in recent years that the ingestion of sodium chloride, especially at the higher levels to which humans have become accustomed, has deleterious effects, mainly related to the cardiovascular system, e.g., high blood pressure and arteriosclerosis. Such ingestion has also been shown to also encourage the growth of tumors. Efforts to restrict the ingestion of salt by eating low or unsalted food or substitute alternate condiments for salt has not been very successful. Therefore, it is preferred to develop non-toxic compounds which counteract the effects of salt and which can be ingested separately or along with the salt.

U.S. Pat. No. 4,499,078 suggests one method for achieving this result. The patent discloses that the anabolic effects of salt on a human body can be reduced by ingesting a compound which has an catabolic action. Specifically, the patent discloses that a magnesium compound containing bivalent negative sulfur may be taken with the salt or separately to offset the effects of the salt on the body. The content of that patent is expressly incorporated by reference herein.

The present invention relates to an improvement in such compounds for more effective counteraction of the deleterious effects of sodium chloride on the body, particularly with regard to the effect of sodium chloride on neoplastic diseases.

SUMMARY OF THE INVENTION

The invention relates to a composition comprising the combination of at least one compound containing a cation of magnesium, calcium, or strontium and an anion of bivalent negative sulfur or selenium, and at least one compound containing a cation of lithium or potassium and an anion of bivalent negative sulfur or selenium. A preferred bivalent negative sulfur is a thiosulfate or thiocyanate anion, and these compositions may also contain a compound

containing a fluoride, silicon or oxygen anion. Advantageously, the magnesium, calcium or strontium compounds are present in an amount of about 2:1 to 20:1 of the lithium or potassium compounds.

The invention also relates to a composition comprising the combination of at least one of magnesium, calcium or strontium thiosulfate, at least one of magnesium, calcium, or strontium thiocyanate, and at least one of lithium or potassium thiosulfate. In this composition, the relative amounts of magnesium, calcium and strontium thiosulfate to magnesium calcium, and strontium thiocyanate to lithium or potassium thiosulfate ranges from about 2:1:1 to about 20:3:1. The composition can also include lithium or potassium fluoride.

An other embodiment of the invention includes compositions of sodium chloride along with the compounds described hereinabove. In these mixtures, the sodium chloride is present in an amount of about 66 to 90 weight percent and preferably between about 75 and 85 weight percent of the composition.

The invention also contemplates a method for counteracting the adverse effects of sodium chloride on the human body which comprises administering to the body one of the compositions described above. These compositions may or may not contain salt.

In this method, the amount of composition to be administered ranges from between 0.5 and 10% by weight, and preferably about 2%, in a water solution.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In U.S. Pat. No. 4,499,078, it was established that the biological activity of various compounds with the body can be classified as either anabolic (constructive) or catabolic (destructive). It was also shown that sodium chloride has an anabolic effect, whereas compounds containing bivalent negative sulfur have a catabolic effect. Thus, the anabolic effect of the sulfur counteracts the anabolic effect of the sodium chloride. The manifest action of sodium chloride upon the appearance and growth of cancers has been established through several experiments. Tumors were produced by a transplant into the hind leg of rats and mice. These tumors were found to grow larger and more rapidly when the animals also received sodium chloride in their drinking water. The size and growth of the resultant tumors caused the animals to die earlier than those who did not ingest the salt.

In groups of 100 exbreeder mice of the strain FC1, the number of spontaneous mammary tumors and the death from other conditions was recorded, during a one year observation. Spontaneous cancer was shown to be increased by the salt intake. In untreated animals, considered as controls, the average for 100 animals in one year observation was around 44% of spontaneous mammary cancers and of 15% death from other conditions than cancer. The addition of 2% salt in drinking water increased the spontaneous cancer to 65% for one year and a mortality of 20% from other conditions.

In animals injected intramuscularly with the carcinogens methylcholanthrene or benzyprene, the number of positive results was not only markedly increased but the tumors appeared earlier when the animals also ingested salt.

All these experiments are indicative of a marked enhancement upon the appearance, growth

and malignant evolution of cancer by the action of ingested sodium chloride

Statistical studies have also shown a relationship between the high intake of salt and arteriosclerosis. U.S. Pat. No. 4,499,078 showed that, in New Zealand rabbits, the intake of 2 g of cholesterol daily induced the appearance of aortic atheromatosis, and that the addition of salt in the drinking water increases the appearance of such atheromas.

The fact is that the diet of people in civilized countries includes an amount of salt which is about ten times higher than the amount considered to be necessary physiologically. Thus, applicant believes that the high occurrence of arteriosclerosis and even cancer may be at least partially attributed to this high sodium chloride intake.

A study of the biological action of the elements has shown the existence of antagonistic actions according to their reciprocal characters and position in the periodic table.

Besides the antagonism between the anabolic and catabolic elements which is related to the different series to which they belong, other antagonistic actions occur between elements in following positions in the same series. In the specific case of sodium, the first antagonism is seen for the catabolic elements, while the second for potassium and lithium, as immediately inferior and superior elements in the same A-1 series. Thus, in such a case a biological antagonistic action is found to correspond to the following cations: magnesium, calcium, strontium, potassium and lithium. Chlorine antagonists include the bivalent negative sulfur, bivalent negative selenium, silicon, fluorine and oxygen.

Especially active antagonists of the sodium chloride are the thiosulfates, thiocyanates, fluorides and chlorates of magnesium, calcium, strontium, potassium and lithium. To these, sodium or potassium chlorate may also be added due to their available oxygen.

Research has shown that each of these preparations has a salutary effect upon the noxious manifestations of the sodium chloride in cancer and arteriosclerosis.

While each one of these products has shown favorable effects by itself in the different experiments for counteracting the noxious effect of the administration of salt in cancer and arteriosclerosis, the concommitant use of two or more of these agents have shown improved results through what is believe to be synergistic action.

The antisodium agents are used as such or added to the salt preparations, and used together. Taste, smell and water solubility are the main criteria for choosing from the different compounds, those which are not changing the qualities of the salt when added to it.

It has been found that at least two of these agents in combination are very effective for counteracting the effects of salt. While any combination of bivalent negative sulfur containing compounds can be used, the most advantageous compounds to date are those containing a combination of nontoxic thiosulfates and thiocyanates. Preferably, at least one Group II thiosulfate or thiocyanate should be combined with at least one Group I thiosulfate or thiocyanate.

Specifically, the combination of magnesium or calcium thiosulfate or thiocyanate with either strontium, potassium or lithium thiosulfate or thiocyanate has been found to be suitable for preparing formulations of this additive. Also combinations of these components can be varied

or mixed to provide additional formulations which would be suitable.

The following formulas were seen to give particularly good results:

Proportion (percent)
Component Agent A Agent B
Magnesium thiosulfate
6 10
Magnesium thiocyanate
3 3
Calcium thiosulfate
3 3
Strontium thiosulfate
1 1
Potassium thiosulfate
2 2
Lithium fluoride 0.03 0.05
Sodium chloride balance balance

In experiments using rats with Furth tumors transplanted in the hind leg, the administration of 2% salt in drinking water has increased the tumors (with an average, for 10 rats), to 30% more than in the untreated control rats. The use of a 2% mixture of the salt plus the antisodium chloride agents -- has induced a manifest reduction of the tumor even with 10% below the controls without salt and of more than 35% for those having received sodium chloride alone. This action was markedly more manifest with the administration of the complex than with any compound alone, when added to the salt. From these experiments it has appeared advisable to use the modified salt to replace ordinary salt.

Mice and rats which received either of the specific complex salts listed above in drinking water for over 6 months did not exhibit any side effects. When these solutions were given to young animals, their growth was not observed to be different from that of the control group (i.e. -- those which received no solution).

Based upon these experiments in animals, the continuous use of the corrected salt may have a basic influence upon both cancer and arteriosclerosis in humans as well.

Method for eliminating or reducing the desire for smoking
US4596706

A method for treating or aiding in the treatment of a tobacco habit or addiction in a human by controlling the craving for tobacco or controlling tobacco withdrawal symptoms which comprises internally administering to said human an effective amount of a compound having an active ingredient containing at least one bivalent negative sulfur to control said craving or said withdrawal symptoms so as to reduce the desire for tobacco.

TECHNICAL FIELD

The invention relates to a method for eliminating or reducing the desire to smoke through the

administration of catabolic sulfur-containing compounds.

DESCRIPTION OF THE PRIOR ART

Sulfurized polyunsaturated oils, or sulfurized oils are disclosed in a book entitled RESEARCH IN PHYSIOPATHOLOGY AS BASIS OF GUIDED CHEMOTHERAPY by Emanual Revici, M.D., published by D. Van Nostrand Co., Inc., 1961, pages 334 and 335. A method of preparing sulfurized polyunsaturated oils referred to in the book as hydro persulfides is set forth in Note 7, page 711 of the book. This book does not disclose however, the use of these sulfurized compounds for preventing or reducing the desire for smoking tobacco as claimed herein. Further, U.S. Pat. No. 4,416,869 discloses a method for preventing or reducing the desire for smoking tobacco in humans by the internal administration of a composition produced by heating certain allylically unsaturated compounds which are sufficient to substantially increase the peroxide titer. The incorporation of sulfur into the composition during this heating process has been found to be particularly advantageous. This patent is expressly incorporated herein by reference.

Applicant has now discovered that a number of additional compounds are effective for eliminating or reducing the desire for smoking.

SUMMARY OF THE INVENTION

The invention relates to a method for treating or aiding in the treatment of a tobacco habit or addiction in a human by controlling the craving for tobacco or by controlling tobacco withdrawal symptoms by internally administering a compound with an active ingredient containing at least one bivalent negative sulfur in an amount effective to control the craving or the withdrawal symptoms.

The most clinically effective anti-smoking compounds for use as an active ingredient are hydropersulfides, alkyl sulfides, colloidal sulfur, organic thio compounds or their pharmaceutically acceptable salts. The most effective thio compounds have proven to be thioglycerols, thioglycols or their pharmaceutically acceptable salts.

These compounds are amenable to oral administration into the human body by mixing the active ingredient with suitable binders and bulking materials and placing an amount of the active material which is equal to a therapeutic dosage level into a pharmaceutical capsule.

The preferred theraputic dosage level is 100 milligrams of the active ingredient and the subject should be instructed to ingest a sufficient number of capsules so as to effect a cessation or reduction in his desire to smoke. The active ingredient may also be administered however, by means of an injection, which allows the sulfur compound to work faster initally. The most clinically effective active ingredient is ethylene trithiocarbonate, thioglycerols, and thioglycol.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It is desirable to have a technique for treating or aiding in the treatment of the tobacco habit or addiction in a human by means of a method for controlling the craving for tobacco and/or by reducing or controlling the symptoms of withdrawal. The invention disclosed herein relates to such methods of treatment.

Testing of the products produced by tobacco smoking shows them to possess, in general, a manifest anabolic action. These studies have concerned the fluorescence of the products found in the tobacco smoke and have disclosed the presence of carcinogenic agents which emit energy. Applicant has discovered that the administration of catabolic agents to a human subject, which agents are antagonistic to the anabolic effects of tobacco by-products, is an extremely satisfactory technique for counteracting the subject's desire to smoke.

The applicant has also discovered that certain catabolic agents, especially active at higher levels of the body organization, are more specifically active than others against the physiological changes induced by smoking tobacco. The preferred catabolic agents for performing this function are bivalent negative sulfur compounds which experimentation has shown to be most efficacious. The following specific compounds have been found to be particularly effective in clinical tests for eliminating or reducing the desire for smoking: hydropersulfides, alkyl sulfides, colloidal sulfur and organic thio products, which include but is not limited to thioglycerols and thioglycols, or other pharmaceutically acceptable salts. Applicant has found that the best results are obtained through the use of the thioglycols thisglycerols and, specifically, ethylene trithiocarbonate.

As an alternate embodiment of the present invention, the compounds disclosed herein, may also be mixed with the compounds disclosed in U.S. Pat. No. 4,416,869.

The method of administration for these compounds may be either oral or parenteral and the intended effect, that of diminishing the subject's desire to smoke, may be obtained even after only one of two administrations of these agents. For purpose of the preferred oral note of administration, the active material may be mixed with binders and bulking agents and therapeutic dosages such as 100 milligrams, may be placed in pharmaceutical capsule for dispensing to a subject.

The dosage prescribed to a patient will, of course, vary depending upon the particular patient and the number of cigarettes being smoked per day. In general a daily dosage should consist of about 3-5 capsules containing 100 mg. each of the active ingredient for the first three days after which the dosage level should be progressively reduced in accordance with the subject's reduced desire to smoke. As noted, however, smoking patterns vary and a heavy smoker may require as many as eight capsules per day for the first three days which could then be reduced to 3-4 capsules per day for the next four days. This is generally sufficient to eliminate or reduce a smoker's desire or need for tobacco. A single course of treatment may retain its effect for months but the smoker may also be provided with a supply of the capsules in case the desire for tobacco returns.

Method for treating the effects of alcohol
US4565689

A method for treating or aiding in the treatment of the manifestations of alcoholism or alcohol intoxication by aiding in the control of the craving for alcohol or by aiding in the control of alcohol withdrawal symptoms, or by aiding in the control of alcohol intoxication in a human which comprises internally administering to said human an effective amount of a compound having an active ingredient containing at least one bivalent negative sulfur to

control said craving, symptoms, or intoxication so as to counteract the effects of alcohol.

TECHNICAL FIELD

The invention relates to a method for eliminating or reducing the noxious effects of alcohol through the administration of catabolic sulfur-containing compounds.

DESCRIPTION OF THE PRIOR ART

There has been much recent interest in the study of alcoholism involving biological, psychological, and sociological investigations. Publications such as the various "Proceedings of the . . . Annual Alcoholism Conference" and "Recent advances in Studies of Alcoholism", obtainable from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, indicate the rather intensive scientific investigations in this area.

An article by E. B. Truitt and M. J. Walsh appearing at p. 100 et sequa of "Proceedings of the First Annual Alcoholism Conference of the National Institute on Alcohol Abuse and Alcoholism", DHEW Publication No. (NIH) 74-675 (1973) discloses a number of chemicals and drugs which have been reported to have anti-alcohol effects. Included in this list are disulfuram (tetraethylthiuram disulfide--see also U.S. Pat. No. 2,567,814 Jacobsen et al), calcium carbimide (see also U.S. Pat. No. 2,998,350 de Grunigen et al), and thiocyanates which are used specifically for their anti-alcohol properties.

U.S. Pat. No. 3,860,719 to Marshall discloses the use of 2-[3,4-dichlorophenoxy)methyl]-2-imidazoline hydrochlorine (fenmetozole HC1) for combatting ethanol intoxication in mammals.

However, an article by H. B. McNamee et al "Fenmetozole in Acute Alcohol Intoxication in Man", Clinical Pharmacology and Therapeutics Vol. 17, Number 6, pp. 735-737 concludes that, within the scope of the subject study, fenmetozole does not antagonize or significantly modify acute effects of alcohol intoxification in humans.

Another publication entitled "Testing For a `Sobering Pill`" DOT HS-801 288 (1974) available from National Technical Information Service, Springfield, Va. 22151 discloses that nikethamide, propranolol, L-dopa, pipradrol, aminophylline, ephedrine, sted-eze, and ammonium chloride were investigated to determine their potential for blocking or neutralizing the effect of alcohol on a human brain; the most effective amethystic agent found was L-dopa.

J. L. Mottin, in an article entitled "Drug-Induced Attenuation of Alcohol Consumption" Quart J. Stud. Alc. 34: 444-472 (1973) discussed, inter alia, the use of the following compounds re the subject title: disulfuram, citrated calcium cyanamide, and metronidazole.

Russian Inventor's Certificate 187250 discloses the use of the "thiolic" preparations--"unitol" and "dicaptol"--for use in treating alcoholism. The Merck Index (Eighth Edition) discloses that Dicaptol (BAL or British Anti-Lewisite) is 2,3-dimercaptopropanol and is marketed as a 10% solution in peanut oil with 20% benzyl benzoate. It is further asserted that in the U.S.S.R. a water soluble form is available under the name Unithiol and is 2,3-dimercapto-1-propanol sodium sulfonate.

U.S. Pat. No. 2,799,619 to Seifter et al. discloses compositions comprising certain phenothiazines as effective for treatment of alcoholics while British Pat. No. 1,399,992 (Revici) discloses that compositions comprising certain organic ethers are useful for the treatment of alcoholism.

U.S. Pat. No. 4,346,082, granted to the applicant on Aug. 24, 1982 discloses a method of treating alcoholism and for eliminating, reducing or preventing alcohol intoxication in humans by internally administering a therapeutic composition comprising an ammonium compound or compounds having a pH greater than 5.0 when placed in aqueous solution at a concentration of 5 grams per 100 grams of solution, and particularly, ammonium salt compounds comprising ammonium cations and sulfur anions.

Further U.S. Pat. No. 4,368,206, issued to applicant on Jan. 11, 1983 discloses an alternate method of treating alcoholism and for aiding in controlling alcohol intoxication in humans by the internal administration of a composition produced by heating certain allylically unsaturated compounds sufficient to substantially increase the peroxide titer. The incorporation of sulfur into these compositions during the heating process was found to be particularly advantageous.

Applicant has now discovered that a number of additional compounds are effective for treating the effects of alcohol.

SUMMARY OF THE INVENTION

The invention relates to a method for treating or aiding in the treatment of the manifestations of alcoholism or alcohol addiction by aiding in the control of the craving for alcohol or by aiding in the control of alcohol withdrawal symptoms or by aiding in the control of alcohol intoxification in a human by internally administering a compound with an active ingredient containing at least one bivalent negative sulfur in an amount sufficient to control the craving for alcohol or the symptoms caused by abstaining from it.

The most clinically effective compounds for this purpose are the hydropersulfides, alkyl sulfides, colloidal sulfur and organic thio compounds or their pharmaceutically acceptable salts. The most effective thio compounds to date are the thioglycerols and ethylenetrithio carbonate or their pharmaceutically acceptable salts.

These compounds are amenable to oral administration into the human body by mixing it with suitable binders or bulking materials, and placing an amount of the active material which is equal to a therapeutic dosage level into a pharmaceutical capsule.

The preferred therapeutic dosage level is about 100 milligrams of the active ingredient and the subject should be instructed to ingest a sufficient number of capsules to reduce or eliminate the desire to drink or to reduce or eliminate the affects of alcohol. The active ingredient may also be administered, however, by means of an injection, which allows the active ingredient to work more quickly, initially. The most clinically effective active ingredient is ethylene trithio carbonate and thioglycerols.

DETAIILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It is desirable to have a method for treating or aiding in the treatment of alcoholism in a

human by controlling the craving for alcohol, by controlling withdrawal symptons, or by aiding in the control of alcohol intoxication by humans. It is further desirable to have a method for aiding the control of alcohol intoxication of a non-alcoholic person by reducing or eliminating the effects alcohol intoxication upon him as well.

A series of tests run on alcoholic compounds by the applicant has shown them to possess a manifest anabolic action, due to the presence of a positively charged hydroxyl (OH) group. This anabolic action is also due to the solubility of the alcohols in lipids, which are fatty substances found in the human body. Due to the small number of carbon atoms which form the organic structure of ethyl alcohol (CH3 CH2 OH) and of other alcohols present in alcoholic beverages, the anabolic action referred to hereinabove is manifested at the higher levels of the body's hierarchic organization, i.e., mainly the organic and systemic levels.

Alcoholic compounds induce the typical anabolic manifestations, which include a preliminary excitation stage followed by a relaxant stage. The applicant has discovered that the adminstration of catabolic agent to a human subject, which is antigonistic to the anobolic effect of alcohol, is an extremely satisfactory technique for counteracting the subject's desire to drink. These agents therefore are indicated for the treatment of all of the manifestations following the intake of alcohol.

The applicant has discovered that certain catabolic agents, especially those active at higher levels of the body organization, are more specifically active than others against the physcological changes which occur in a human subject subsequent to the consumption of alcohol. The preferred catabolic agents for performing this function are bivalent negative sulfur compounds which clinical testing has shown to be the most efficacious agents.

The following specific compounds have been found to be particularly effective in clinical tests for eliminating or reducing the effects of alcohol consumption: hydropersulfides, alkyl sulfides, colloidal sulfur and organic thio products, mainly thioglycerols and ethylene trithio carbonate. The applicant's invention should not, however, be limited solely to the compounds listed above. The applicant has found that the most favorable results occur with the use of ethylene trithiocarbonate. The method for administration of these compounds may be through either the oral or parenteral route and it is important to note that the antianabolic action of these compounds is also manifested by an actual reduction in the amount of alcohol present in the blood of the subject. The dosage prescribed to a patient will, of course, vary depending upon the physical size and physiological characteristics of a particular patient and, since drinking patterns vary, the amount of alcohol consumed must also be taken into account in determining the correct dosage.

Generally speaking, however, for purposes of the preferred oral route of administration, the active material may be mixed with acceptable binders and bulking agents and therapeutic dosages of 100 milligrams, may then be placed in phamaceutical capsules for dispensing to a subject. For the average individual, a daily dosage of about 3-5 capsules containing 100 milligrams each of the active ingredient for the first 3 days after which the dosage level would be progressively lowered in accordance with the subject's reduced desire to drink. A heavy drinker may require as many as 8 capsules per day for the first 3-4 days, which could then be reduced to 3-4 capsules per day for the next four days. This should be a sufficient dosage to eliminate or reduce the subject's need for alcohol or to reduce or eliminate its effects after consumption.

As an alternate embodiment of the present invention, the compounds disclosed hrein may also be mixed with the compounds disclosed in U.S. Pat. No. 4,368,206. Therefore, the teachings of this patent are expressly incorporated herein.

Method for treating drug addiction
US4565690

A method for treating drug addiction from compounds which cause a catabolic effect on the human body, which comprises administering to said body, a sufficient amount of an anabolic agent containing bivalent negative selenium or sulfur.

TECHNICAL FIELD

The invention relates to methods and compositions for treating drug addiction, particularly for the treatment of the symptoms of withdrawal when the patient terminates using drugs.

BACKGROUND ART

In treating patients for drug addiction, the most common method employed is that of allowing the patient to "dry out" or eliminate the drug from their system. This period, called withdrawal, is a very difficult time for the patient, since the body is in need of the drug due to its previous habitual use and dependence thereon.

It was previously not recognized that the effect of the drug on the body would be counteracted by administering a compound which produces an opposite effect on the body so as to offset and neutralize the detrimental defense effects of the body. The present invention provides one such solution for this problem.

SUMMARY OF THE INVENTION

The invention relates to a method for treating drug addiction from compounds which cause a catabolic fatty acids defense effect on the human body, which comprises administering to said body, a sufficient amount of antifatty acids agents, preferred antifatty acid agents includes a variety of agents comprised of selenium and sulfur compounds. The active ingredient of these agents can be administered orally or by injection. Preferred dosages include about 10 ml of the oil (about 0.5 to 1 gram).%

The invention also relates to a method for treating drug addiction from compounds which cause a catabolic noxious effect on the human body, which comprises admistering to said body, a sufficient amount of antifatty acid agents.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

My study concerning drug addiction and the symptoms of withdrawal is based on the recognition of a dualism, in the pathogenisis of the condition and the action of such agents on the human body. This dualism is shown in the antagonistics of the anabolic-constructive and catabolic-destructive conditions, of such agents. In the pathogenesis of the anabolic condition, abnormal sterols intervene while in the pathogenisis of the catabolic condition,

abnormal fatty acids having as characteristic the presence of trienic conjugated formations intervene. Clinically, these catabolic conditions are observed as insomnia, diarrhea, vomiting, cramps, generalized are localized pair, particularly in the bones and joints, horiplations and tremors in the patent. The stronger the catabolic condition of the drug agent the more intensive the clinic manifestations.

In order to determine whether the agents are either anabolic or catabolic in effect, an entire series of tests must be conducted. In the test of pH of second day wound crust, an anabolic agent induces a lower pH, while a catabolic agent produces a higher pH. In the study of the curve of healing wounds, an anabolic agent makes any peaks disappear, while the catabolic agent increases a leukocytosis, eosinophilia, a lowering of the serum potassium and more free water, while the catabolic agent causes directly opposite changes. In higher specific gravity, a lowering of the chlorides and of calcium excretion.

By applying this research to the problem of any addiction it was found that the agents which induce an addiction have typical anabolic characters, and their action induces a typical anabolic imbalance.

By applying the influence exerted by these various agents upon the oxygen uptake of cancer cells, suspension or yeast, using the YST oxygen monitor, it was found that, over a period of time, the anabolic agents reduced the uptake of oxygen, while the catabolic agents increased it. However, for the anabolic agents, their initial action caused an increase in the oxygen uptake was taking place. This paradoxical action was induced in fact by the action of low amounts of the active agent. This paradoxical action seen in the oxygen uptake test also explains the clinical action with two phases for the addictive drugs studied. The first phase corresponds to a cerebral excitration, followed by the second, of deep sleep, corresponding to a typical anabolic action. This is seen for the narcotics with a primary excitation, followed by deep sleep.

The recognition of the typical anabolic character for the addicting drugs, represents the first fundamental discovery for the treatment of this problem.

In a study of body defenses, I found that the body defends itself against an anabolic agent which is repeatedly introduced, by manufacturing antagonistic lipids having a catabolic character--i.e., fatty acids. The abnormal nature of these fatty acids is due to the presence of trienic conjugated formations. The defense character of these fatty acids appears in two ways. First, in their relationship with the anabolic drug, which corresponds to a reciprocal neutralization whereby the fatty acids neutralize the anabolic drug, while the anabolic drug neutralizes the noxious action of the abnormal fatty acids. Also, due to its defense character, the body has a tendency to increase its manufacture of the necessary neutralization agents. Due to this reciprocal neutralization, the presence of an excess of the defensive fatty acids requires the need for the drug in order to neutralize it. The more drugs introduced, the more fatty acids are manufactured in a defense action; the more fatty acids are present, the more the need for the drug to neutralize them. This explains the two manifest characters of addiction, the appearance of the need for the drug, and the progressive increase of this need.

In withdrawal, the high amount of the catabolic defense fatty acids remains in the body, since they do not have the anabolic drug to neutralize them. It is the presence of these fatty acids which induce the manifestations of withdrawal. The symptoms are typically catabolic as occur due to the action of the abnormal fatty acids; i.e., insomnia, diarrhea, vomiting, cramps,

perspiration, pain in the bones, and horipilations. Dienic and trienic conjugated formations are found through spectral analysis present in the urines. Analytical data of blood and urine show the presence of such catabolic conditions. The presence of an urinary strong alkalosis indicates the presence of this catabolic imbalance directly affecting the systemic level.

The recognition of a catabolic imbalance, due to the presence of high amounts of noncompensated abnormal fatty acids, constitutes the main character of the drug withdrawal condition. An action upon these fatty acids represents the consequent therapeutic intervention.

Numerous means to act upon these abnormal trienic conjugated fatty acids have now been discovered. In one, an oxidation of the abnormal fatty acids was considered. In the study of the actions upon such fatty acids, it appears interesting to note their oxidating change under specific conditions. Several specific characters have been found to effect this change. In one, the agent has a lipidic character. This appeared to be effective due to the affinity between lipids and the primary character of the fatty acids which are lipids.

The action of selenium was also found to work well when used in the bivalent negative state. I found a fundamental difference between bivalent negative and tetra and hexavalent positive selenium. The bivalent negative selenium has an oxidation character similar to that of the minus 2 of oxygen, and has different effectiveness than the tetra or hexavalent positive oxidation states.

Furthermore, preparations having bivalent negative selenium and lipidic characters are preferred. For this aim, a method for introducing these elements into unsaturated fatty acids was developed.

By heating an oil, such as an unsaturated fatty acid or a mixture of them, at a critical temperature, the double bonds open. At this place, therefor, an element can be attached. For a bivalent negative selenium the result of this attachment of one atom corresponds to an epoxy, while two atoms correspond to a peroxy, depending upon the exact temperatures used.

According to the invention, a mixture of a vegetable oil and gray or red selenium is heated until the selenium is incorporated. This occurs around 215 DEG C., when the solution becomes clear. Polyunsatured vegetable oils have been found to be the most advantageous for use in the invention.

A preferred polyunsatured vegetable oil is sesame seed oil, although any naturally occurring vegetable, animal or fish oil can be utilized. Alternately, the same mixture can be heated to above 240 DEG C. until foaming has ceased. Either of these two preparations can be used separately or preferably mixed together. The preferred route of administration is by intramuscular injection. These preparation whether used separately or in combination, have been shown to possess an extemely low toxicity in both animals and humans.

In very severe cases of withdrawal, from methadone for example, a number of doses of from 0.5 to 1 gram % selenium in this oil were injected per day, and this without any subjective or objective side effects. In general, much lower doses are preferred in order to induce an efficient detoxification. The doses are indicated by the clinical response of the patient, and they may be increased if any withdrawal symptoms remain. It is preferable to prevent any withdrawal symptoms from occurring in the patient.

The changes in the patient were evident in the blood analyses. The original withdrawal symptoms were unusually controlled by a single injection of about 10 ml, the effect is being seen within 45 minutes. A treatment of several days is necessary to obtain a good detoxification which would continue as long as the subject did not again take the addicting drugs.

Members of the following groups of agents represent other compositions to treat or intervene in the treatment of drug withdrawal by acting upon these abnormal fatty acids. They may be used alone or preferably in combination with the selenium-oil mixture. The agents are lipoidal in character, i.e., they are more soluble in neutral solvents than in water so that they act directly upon the fatty acids.

Such groups include: selenium as a bivalent negative liposoluble compounds, such as organic selenides and selenium incorporated in fatty acids; sulfur as colloidal sulfur; crystals from sulfurized or selenized oil; thiosulfates; thioglycerols; thioglycols; ethylene trithio carbonate; organic lipidic bivalent negative sulfides, disulfides, mercaptans; lipidic compounds or incorporated in oils or fatty acids; lipsoluble ethers, preferably butyl ether and butyl-oxy-phenyl ether; fatty alcohols and also these obtained as mixtures, by treating the fatty acids of animal or vegetable oils with lithium-aluminum-hydride.

Sterols obtained especially as unsaponifiable fractions from fats, oils, organs, organism or other biological material, i.e., more soluble in neutral solvents than in water. Other groups are the lipidic alcohols, i.e., those which are more soluble in neutral solvents than in water, such as pentanol, heptanol, 3-pentanol and 3-heptanol, pentyl and heptylamines and especially 3-heptylamine. Lipidic aminoalcohols, liposoluble epoxide and peroxides; the anabolic elements of the 1A, 111 A, VA, V11 A, 11 B, 1V B, V1 B, and iron and nickel series, and liposoluble corticoids are also useful according to the invention. With adequate or sufficient amounts, favorable action was obtained with members of each group.

It has appeared advantageous to use combinations of members of more than one group, and this reduced the inherent side effects of each agent. Most advantageously, these combinations should be used together with the selenium incorporated in oil.

The clinical applications show the need to have the treatment continued for several days after all the symptoms of withdrawal have fully disappeared. This is done in order to control the natural body tendency to continue to manufacture the abnormal fatty acids as a defensive action.

Treatment of symptoms of neoplastic diseases
US4624851

The method of treating neoplasms in lower animals and humans by administering thereto fluorine containing acids or their non-toxic salts or esters.

The present invention is concerned with a method of treating the symptoms of neoplastic diseases and more particularly, the use of fluorine containing acids for alleviating symptoms of neoplastic diseases without treating the disease itself.

The fluorine containing acid that can be administered to the body for alleviating symptoms of neoplastic conditions without treating the disease itself include perfluorobutyric acid, perfluoroglutamic acid, perfluorooctanoic acid, perfluoropropionic acid, perfluorosuccinic acid, hexafluorophosphoric acid, fluoroacetic acid, fluorobenzoic acid, fluoromethylbenzoic acid, and fluorosulfuric acid. The above fluoroacids are given as representative and the invention does not exclude the use of other fluorine containing acids. The non-toxic salts of esters of the fluorine containing acids can also be employed. The ammonia (NH_3) salts are at present perferred. The organic fluorine containing acid can contain various amounts of fluorine atoms, however, a significant decrease in activity appears to result when these acids contain 20 or more fluorine atoms. It is thus advantageous to employ fluorine containing organic acids having less fluorine atoms. Best results to date are obtained with perfluorooctanoic acid and hexafluorophosphoric acid, particularly their ammonium salts. The fluorine containing acids can also be used in admixtures with each other.

The fluorine containing acids can be water soluble or water insoluble and either can be used directly in solution, e.g., water or alcohol, or in conventional therapeutic emulsion form.

The required dosage will, of course, depend upon the particular fluorine containing acid being employed as well as the extent of the neoplasm in the patient. Generally, especially with hexafluorophosphoric acid, from about 100 mcg. to 50 milligrams is sufficient. The appearance of a slight dizziness is a factor limiting the use of progressively increasing dosages. The treatment can be continued at various intervals, preferably daily, until maximum effect is obtained. Administration can be orally or by injection.

No claim is made that the use of fluorine containing acids will cure neoplasms but subjective improvements result in various symptoms of neoplastic conditions, such as cancers, sarcomas, lymphomas, leukemias as well as in benign tumors. The use of the fluorine containing acids is noted to reduce pain and alleviate other known symptoms of neoplastic conditions. The invention is useful for treating symptoms of neoplasms in the lower animals as well as in humans.

Method for the treatment of acquired immune deficiency syndrome US5153221

A method and composition for the treatment of a patient with AIDS. The composition comprises an AIDS-symptom alleviating effective amount of an aliphatic carboxylic acid having an odd number of carbon atoms and containing at least 5 and not more than 10 carbon atoms. The composition may be administered in a pharmaceutically acceptable oily carrier and is administered orally and/or by intramuscular injection.

BACKGROUND OF THE INVENTION

The study of the pathogenic factors of diseases caused by the HIV virus, e.g., the acquired immune deficiency syndrome (AIDS), has shown that, in addition to the presence of the virus, parasitated lymphocytes which have been infected by the virus are present which represent the detectable lesions of the of the disease. Accordingly, in a therapeutic approach to this disease, an attempt to destroy the parasitated lymphocytes must be considered, in

addition to treatment having a direct antiviral action.

Studies of the parasitated or infected lymphocytes has shown that they, like other lesions in the body, contain free lipids. They are especially sensitive to the action of agents having a lipidic character when introduced into the body.

SUMMARY OF THE INVENTION

I have discovered that certain lipidic agents have a specific capacity to act upon the pathogenic factor of AIDS. These agents act upon the virus itself, as well as the infected or parasitated lymphocytes. In particular, I have discovered that aliphatic organic compounds having five or more carbons and a lipidic character, i.e., are soluble in unpolarized or organic solvents rather than water, provide an effective procedure for the treatment of AIDS. These compounds appear to be bound by the viruses and the parasitated lymphocytes through the free lipids of the virus and lymphocytes.

More specifically, I have found that compounds having a negative polar group and, especially, an acidic polar group, exhibit a characteristic antiviral activity and effect in decreasing the number of parasitated lymphocytes.

The method of the invention comprises administering to a patient with AIDS, an anti-AIDS symptom reducing effective amount of an organic aliphatic acid having at least 5 carbon atoms and an odd number of carbon atoms.

DETAILED DESCRIPTION OF THE INVENTION

Organic acids particularly suitable for use with the present invention are pentanoic, nonanoic and heptanoic acid. Most preferred is heptanoic acid. Each of these compounds exhibit not only anti-HIV virus effects, but also affect the parasitated or infected lymphocytes, killing them.

The compounds are administered intramuscularly or orally from oily solutions. Conventional organic oils which are pharmaceutically acceptable may be used as the oily carrier. Typically, for example, vegetable oils, and most preferably, polyunsaturated oil, such as, safflower oil, are suitable. For oral administration, a solution having a concentration from about 20 to 60%, and preferably, about 50% and in amounts of from about 1 to 5 ml per dosage, two to four times a day, are effective. For intramuscular injection, oily solutions having concentrations up to 30% acid may be used with injection volumes being from about 2 to 10 ml per injection, one to four times per day. (All concentrations are expressed as volume/volume percent.) I have found that these administrations are well tolerated. The inventive method may be utilized with oral or intramuscular injection alone or in combination. The administration of the medicament may be continued for as long as necessary.

Toxicity studies with these acids have shown that they are essentially non-toxic in mice after repeated injections of 0.5 ml of a 10% volume/volume solution for more than two months. No toxic effects were observed in rats with daily injections of 1 ml of a 10% volume/volume solution.

In addition, for all of the patients described hereinafter, no complaints of any side effects were received, even when relatively large amounts of medication were administered.

A group of forty AIDS patients was treated utilizing heptanoic acid. The patients were diagnosed as having AIDS by conventional analysis. These patients were each treated orally with heptanoic acid in safflower oil, in 50% oily solution, in doses from 2-5 ml, two to four times a day for more than one month. Impressive subjective changes and improvements in the condition of each of the patients were seen, even beginning after the first administration. No toxic effects after prolonged treatment with higher amounts were observed.

Ten patients diagnosed with AIDS and having chronic diarrhea were treated. These patients had chronic diarrhea for more than month which did not respond to any conventional treatment. They received from 2-5 ml of the 50% heptanoic acid orally in safflower oil, three to four times a day. Using this inventive method, this symptom was fully controlled within a period of less than one week in each of these patients.

This treatment has also produced significant changes in the ratio of helper to suppressor lymphocytes. Generally, the normal ratio of helper to suppressor lympho cytes should be about 1.2. With patients having AIDS, this ratio is as low as 0.1. With the inventive treatment, improvements in increasing this ratio are seen beginning with the initial treatment and continuous improvement has been seen after treatments for a period of one month.

The following are details of two of the forty clinical treatments referred to above.

J. D., 38 years old, with a T4 /T8 ratio of 0.14, exhibited severe manifestations of AIDS, including diarrhea and fever. Within one week of treatment with 3 ml of a 50% volume/volume heptanoic acid in safflower oil, these symptoms were fully controlled. After a two-month treatment of 2 ml of this medication three times a day orally, he remained symptom free for six months without any further treatment. His T4 /R8 ratio remained at a level of about 1.0.

L. S., 24 years old, diagnosed with AIDS. He was rapidly deteriorating for the month prior to his beginning treatment. The manifested symptoms were primarily fatigue, loss of weight, loss of appetite, fever and multiple lymphatic gland involvement. The T4 /T8 ratio was 0.2. Within one week of treatment with 3 ml of 50% volume/volume heptanoic acid in safflower oil, orally four times a day, these symptoms were controlled.

After two months of treatment, the patient has remained in exceptional good clinical condition for the last six months, continuing with the treatment of 1 ml administered once a day. His T4 /T8 ratio remain above 1.0.

In another variant of the present invention, a mixture of 30% heptanoic acid, 15% pentanoic acid, and 15% nonanoic acid (volume/volume percentage) in safflower oil were used orally with from 1 to 3 ml dosages four times a day. Clinical results in 12 patients with varying pathological AIDS manifestations all resulted in substantial improvements of their symptoms.

Selenium compounds having antineoplastic activity, process for the preparation thereof and pharmaceutical compositions therefrom US4564634

Organic compounds of selenium are prepared by reaction of metallic selenium with eleostearic acid under warming. Tung oil may be used. The compounds contain between 0.1 and 5% by weight of selenium. Pharmaceutical compositions having antineoplastic activity are prepared, which contain as the active component, the organic compound of selenium. The method of treatment of animals and humans affected by neoplastic conditions is described.

The present invention relates to new organic compounds of selenium, which exhibit a substantial antineoplastic activity. More specifically, the invention covers compounds prepared by addition of selenium to eleostearic acid. This substance is 9,11,13-octadecatrienoic acid of formula

CH3 --(CH2)3 --CH.dbd.CH--CH.dbd.CH--CH.dbd.CH--(CH2)7 --COOH

This acid is a fatty acid and is the chief component (about 80%) in "tung oil", also called "china wood oil". According to a preferred method for the preparation of the compounds according to the present invention, "tung oil" is used as a source of eleostearic acid. By warming metallic selenium with eleostearic acid, or more appropriately with "tung oil", at a temperature in the range of 200 DEG-250 DEG C., one notices the disappearance of selenium itself with formation of an addition product in which selenium is bound to the chain of the fatty acid with bonds of various nature (for instance a perselenide, or hydroperselenide, or episelenide bond or others).

The percentage of selenium in the compounds prepared in this manner may vary within a very broad range, for instance between 0.1% up to 5%. However, for the therapeutical use, compounds containing 1-2% by weight of selenium are particularly useful.

The invention also relates to the method of preparation of the novel compounds of the invention which comprises warming selenium with "tung oil" up to the point when the mixture becomes clear, that is when the elementary selenium disappears. The following example illustrates the method of preparation according to the invention without, however, limiting the invention in any way.

EXAMPLE

Selenium, either in the gray or red form, three grams finely powdered, is warmed gradually in 100 grams of tung oil under efficient stirring in a bath of dowtherm. At a temperature of about 230 DEG C., the mixture begins to become clear and becomes completely clear at a temperature of about 248 DEG C. This requires about 2-3 hours of heating. After an additional one half-hour of heating while under efficient stirring, the mixture is allowed to cool and the selenium which has not reacted and which has collected as a single clot, is decanted.

The liquid which is obtained contains 2.03% of selenium, the determination being made by atomic absorption. The ultraviolet spectrum of the compound which will be referred to hereinbelow by the symbol "TSel" exhibits absorption maxima typical of conjugated trienes and conjugated dienes. This fact coupled with the determination of the iodine number, which is carried out with sodium thiosulfate and determining the amount of iodine set free in the reaction between TSel and potassium iodide in acetic acid, shows the presence of selenium bound to carbon atoms adjacent the double bond of a triene in the form of a hydroperselenide group (.dbd.C--C--Se--Se--H), and selenium added to a double bond in the form of a

perselenide ##STR1## It should be clarified, however, that the novelty of the invention is not in any way limited to the manner of how the selenium is bound in TSel, or more generally, in the compounds according to the present invention.

The substance TSel thus obtained may be administered as such in the form of drops of 50% diluted with sesame oil and administered in unit dosage form in capsules of gelatine or in phthials for injection. The substance in a 2% concentration of selenium prepared as described hereinabove, has been investigated to determine the acute toxicity, subacute toxicity, chronic toxicity and carcinogenic activity. The results are reported hereinbelow.

Acute Toxicity

The acute toxicity of TSel has been tested in mice and rats of both sexes, treated with increasing doses of TSel administered subcutaneously, intraperitoneally and intragastrically.

By the subcutaneous route, no death has been observed when the substance is administered up to 1 cc of TSel in mice (26-32 g .female. and 28-34 .male.) and up to 2 cc in rats (150-220 g .female. and 170-230 g.male.). By the intraperitoneal route, the maximum doses which have not caused death, are 0.2 cc for female mice, 0.5 cc for male mice and 0.8 cc for rats of both sexes. The maximum doses which have been tested, 1 cc for mice and 1.5 cc for rats, have caused death in at least 50% of the animals with the exception of female mice which have shown to be more sensitive. The autopsy has shown an atrophization of the suprarenal glands with almost a total disappearance of sudanophilic material.

On the other hand, the administration by the intragastric route of the material up to 1 cc in mice and 2 cc in rats of both sexes has not caused toxic symptoms worth mentioning with the exception of the reduction of the sudanophilic material in the suprarenal glands at the higher dosage.

Subacute Toxicity

Subacute toxicity has been studied by administration of increasing doses of TSel for six consecutive days to mice and rats of both sexes by the subcutaneous route and by the intragastric route and in guinea pigs by the intragastric route.

By the subcutaneous route, only at the highest dose of 0.3 cc, there is observed the death in the treated mice, (1/10 in the female and 2/10 in the male) while no pathological symptoms have been observed in rats treated up to 0.3 cc per 100 grams.

The treatment by the intragastric route has caused no toxic symptoms worth mentioning, with the exception of a slight gastritis at the highest doses in the case of mice (0.3 cc) and rats (0.5 cc). The treatment was, on the other hand, tolerated very well by guinea pigs also at the highest dosage of 0.4 cc.

Chronic Toxicity

Mice weighing 30 grams were subjected to a subcutaneous injection in the amount of 0.1 cc per day, three times a week for a period of three consecutive months. The animal presented no abnormal reaction with respect to the controls, nor was any pathological change noted in the animals after they had been killed. An equal result was obtained in the rats treated with

0.2 cc per 100 grams. No toxic reaction was observed by administration of TSel to rats and mice by the oral route by means of a catheter in the dose of 1 cc per day for a prolonged period of time and even after adding 1% of TSel to the feed of the same animals.

On the basis of what has been described hereinabove, the compounds according to the invention are practically non-toxic. This is even more surprising if one considers that compounds of selenium are known to be toxic.

Carcinogenic Activity

Thirty male mice of 23-27 grams weight and 30 female mice weighing 28-31 grams were fed for one year a feed in the form of pellets, each one of them contains 0.1 cc of TSel.

At the end of the period of treatment, no case of neoplastic condition was noted.

Pharmacological Properties

The concept of anabolic-catabolic dualism and relative definitions, as described hereinbelow, is amply illustrated also from an experimental point of view, in the case of lower animals by E. Revici, Research in Physiopathology, Van Nostrand, Ed., Princeton, 1961.

It should be noted, however, that the invention is not based on the correctness of the theoretical considerations discussed in the work by E. Revici.

The compounds according to the present invention exhibit a marked catabolic effect, as shown by a series of tests. The administration of the substances by the oral route or parenteral route to rats, mice, guinea pigs and rabbits, induces a leukopenia below 6000 per cubic millimeter, with an eosinopenia, the value of which is below 60 per cubic millimeter, corresponding to a catabolic action. In addition, in the lower animals one notes an increase of potassium in the serum with a decrease of the same potassium in eritrocytes, always corresponding to a catabolic action.

The substance TSel and the other compounds according to the present invention cause changes in the urine, which may be summarized as follows: lowering of surface tension to below 66 dynes per centimeter; an increase in specific gravity to a point above 1016; lowering of pH to a point below 6, thus always exhibiting a catabolic action.

By means of analyses of atomic absorption, one notes that selenium is uniformly divided in the organism and is reduced in drastic measure in the period of 48 hours following the administration, selenium itself being transported by the erythrocytes mainly and being eliminated through the feces and urine. If the substance TSel is administered to animals having tumors, the analyses of atomic absorption show that 75% of selenium is fixed on the tumors themselves. In addition, about the same amount of selenium is found again in tumors of animals after they have been killed, one or two weeks after administration.

It has been found by the cytochemical analyses that selenium is present almost exclusively in the cytoplasm of cancerous cells. Histological studies have shown a substantial increase in pyknosis and cellular carrhiorexi of cancerous cells with necrotic zones.

In the study of oxygen absorption by ascitic cells of mice suffering from cancer, and oxygen

absorption by yeast, the compounds according to the present invention cause an increase in the absorption itself corresponding to a catabolic action. When administered orally or administered in rats by injection, the compounds according to the present invention, cause a change towards higher pH values in the scab of wounds one day old. Control animals have shown a pH between 7.62 and 7.64, while in other treated animals, the pH reaches 7.80 showing a substantial catabolic action. The study of the effect exerted by the products according to the present invention on the curve of recovery of an epidermic wound in mice and in rats shows also a substantial catabolic action, which is manifested by the substantial increase in peaks and by the prolonged period of recovery.

The oral administration of the compounds according to the present invention, in selected mice of FC1 origin, which in the controls exhibit 45% spontaneous cancer during one year of observation, has shown a reduction of spontaneous cancer to about 8%.

In another group of experiments, the oral administration of TSel for one year, in the dose of 0.2 cc per "pellet" of Purina feed, has been capable of achieving a reduction in the incidence of spontaneous cancer from 40.6% in the controls to 3.3%.

The administration to mice and rats which had undergone a transplant of various tumors has shown a substantial decrease in the percentage of positive results from 100% in the controls to an average of 4% in the treated animals. The administration to animals having transplanted tumors has induced constantly the reduction in growth, and in the case of intramuscular transplant, it has caused the disappearance of tumors administered with compounds to an extent more than 60%.

By way of example, the results obtained in mice in which ascitic cancerous Ehrlich cells had been transplanted, by the intramuscular route are reported hereinbelow.

The animals were treated for six days with an injection of TSel in the dosage indicated hereinbelow.

Antitumoral Activity of TSel; Mice CF1
No. of Animals Sex Dose Tumors

10 .male. -- 10/10
10 .female. -- 10/10
10 .male. 0.05 cc 2/10
10 .male. 0.2 cc 0/10
10 .female. 0.1 cc 0/10
10 .female. 0.3 cc 0/10

Methods for counteracting the deleterious effects of sodium chloride US4499078

A substantially tasteless, non-toxic composition comprising sodium chloride and a magnesium compound containing bivalent negative sulfur and method of using the compositions to control the deleterious effects of large amounts of sodium chloride on the human body.

FIELD OF THE INVENTION

This invention relates to new and useful improvements in a composition and process for reducing the deleterious effects of ingested sodium chloride and, more particularly, relates to a composition or mixture including sodium chloride and a magnesium compound containing bivalent negative sulfur.

BACKGROUND OF THE INVENTION

It has become apparent in recent years that the ingestion of sodium chloride, especially at the higher levels to which humans have become accustomed, has deleterious effects, mainly related to the cardiovascular system, e.g., high blood pressure and arteriosclerosis, but also encourages growth of tumors. Efforts to restrict the ingestion of salt by eating low or unsalted food or substituting condiments has not been very successful.

DESCRIPTION OF THE INVENTION

A study of the biological activity of compounds has shown that they include either destructive-catabolic or constructive-anabolic actions in the human body. The manifestations of an abnormal condition, as symptoms, signs, pathology analyses and response to therapy are related to this dualism. Hypertension, arteriosclerosis and the growth of tumors are recognized as typical constructive anabolic manifestations. On the other hand, I have shown that the action of compounds upon the body has either an anabolic or a catabolic action. Thus, compounds can be classified as anabolic or catabolic by a series of tests.

By tests, such as of the effect on the second day wound crust pH, or on the curve of the healing of a wound, or on the bloor eosinophile leukocytes and potassium, or on the urine pH, surface tension, specific gravity and chloride excretion, compounds can be established as either anabolic constructive or catabolic destructive.

Through the study from this point of view of the biological actions of the elements, I have shown that the members of the different series (vertical grouping) of the periodic table have either anabolic or catabolic actions. The IA series, to which the sodium belongs, has anabolic actions. The same for the IIIA, VA and VIIA, to which the chloride element belongs. Sodium chloride consequently produces high anabolic effects. Oppositely, I have shown that the series IIA, IVA and VIA have antagonistic catabolic effects.

I have further found that the elements of the same period (horizontal grouping) act at the same level of the body organization, such as subnuclear, nuclear, cellular, metazoic or systemic, and that the sodium and the chloride act at the same metazoic level (tissues and organs). The biological effect of sodium chloride is thus a strong anabolic action at the metazoic level. This explains the noxious action upon the blood pressure and arteries, leading to the anabolic-constructive arteriosclerosis.

Following the same systematization of the elements acting at the same metazoic level as the sodium and chloride but having an opposite catabolic action, it appeared that the use of one or more of the catabolic metazoic elements would produce the opposite action of this biological effect of the sodium chloride.

This was shown to be true experimentally. Magnesium was seen to be opposite biologically to sodium, while the sulfur biologically opposite chlorine. In the case of sulfur, it was found that the bivalent negative was more active than the tetra- and hexa-valent positive.

Based on these primary considerations, compounds having magnesium and sulfur were used, in order to show this antagonism as set forth in the following experiments.

The bilateral adrenalectomy in young rats, of below 150 g, was seen to have almost 100% mortality. The administration of 1% solutions of sodium chloride as drinking water was seen to protect the adrenalectomized animals and, if administered for a sufficient length of time, to prevent the death. The administration together with the sodium chloride of magnesium sulfate, the last in subcutaneous repeated injections of 0.5 ml of a 10% solution for 100 g of animal or orally as 1% in drinking water, was seen to be antagonistic to the action of the sodium chloride. In the adrenalectomized animals treated with sodium chloride and magnesium sulfate the mortality was over 80% instead of almost zero for the adrenalectomized animals receiving only the sodium chloride. The same for the older animals, to which the administration of magnesium sulfate (1% in drinking water) was seen to increase the mortality from 20% in controls to 75% in the animals receiving the magnesium sulfate. The use of the magnesium thiosulfate was still more effective than the magnesium sulfate.

The relationship between sodium chloride, magnesium sulfates and arteriosclerosis was seen in the following experiments.

New Zealand rabbits were given 2 grams of cholesterol a day, orally, together with their food. Sacrificed after one month, they showed atheromatous lesions of the aorta. The animals sacrificed after only two weeks of receiving the cholesterol showed only few minimal lesions or none at all. The addition of sodium chloride (3% to the drinking water) to the animals receiving 2 g of cholesterol daily was seen to induce manifest aorta lesions and this after only two weeks of treatment with cholesterol.

The administration of magnesium thiosulfate at 3%, together with the 3% sodium chloride in the drinking water, was seen to prevent the appearance of the aorta lesions, not only after two weeks as in the controls with NaCl alone, but even after one month.

As noted above, antagonism exists between magnesium and sodium which counteracts the biological action of sodium and that the same antagonism exists between the chlorine and sulfur, especially in the bivalent negative state.

It is thus possible to overcome the adverse effects of sodium chloride by adding various magnesium compounds, such as magnesium oxide or magnesium acetylsalicylate and the sulfur compounds separately. Various sulfur compounds or even colloidal sulfur can be used for this purpose. The ingestation of colloidal sulfur has been found to produce sulfides in the intestines of animals. The bond of magnesium to catabolic sulfur enhances this antisodium action. It has been found that the best results are obtained by utilizing a magnesium compound containing bivalent negative sulfur and especially magnesium thiosulfate.

The composition is prepared by merely mixing sodium chloride with magnesium thiosulfate, preferably previously heated around 170 DEG C. in order to eliminate or reduce its hydrated water. The crystals of magnesium thiosulfate are preferably ground to a fine powder before

mixing with sodium chloride. The sodium chloride crystals can also be ground to a fine powder if desired. In this manner the taste of magnesium thiosulfate in the composition is substantially reduced. The amount of magnesium thiosulfate should be at least about 1% by weight of the total composition in order to subsequently antagonize the adverse effects of sodium chloride. Amounts as high as 10% by weight of magnesium thiosulfate can be employed without substantially affecting the taste of the sodium chloride. Amounts as high as 25% by weight could be used where taste is not a factor.

Other catabolic agents, of a lower organizational level of the cells, such as Ca, Sc, V, Mn, Co, Cu, Ge and Se may be added together with the magnesium and sulfur.

Other antianabolic agents, such as vitamins A, D, B6 and B12, fatty acids, aldehydes, and the special group of agents having a twin formation (2 atoms with the same electrical charge bound together) can also be added to the magnesium-sulfur agents if desired.

Virucidal compositions and therapy
US4513008

A method of inactivating enveloped virus comprises contacting said virus with a virucidally effective amount of a C20-24 linear polyunsaturated acid, aldehyde or primary alcohol having 5-7 double bonds, a pharmaceutically acceptable salt of said acid, or a mixture thereof. Topical administration of the virucide is preferred and is effective in treating lesions associated with herpes infections. Pharmaceutical compositions for use in the present method are provided.

BACKGROUND OF THE INVENTION

This invention relates to virucides and in particular to a method of inactivating enveloped virus. In a composition of matter aspect, the invention relates to a pharmaceutical composition for use in the present method.

Viral infections have in the past been largely resistant to antibiotic therapy. In particular, herpes infections have proven to be especially refractory. Herpes virus belongs to the class known as 'enveloped virus", by which is meant those DNA or RNA virus having a lipoprotein envelope. Normally, the virus envelope is derived from host membrane components under the direction of viral protein. The class of enveloped virus includes herpes virus, e.g., herpes simplex 1 and 2; myxovirus, e.g., influenza virus; paramyxovirus, e.g., virus responsible for measles and mumps, and respiratory syncitial virus responsible for croup; corona virus, which is also implicated in the common cold; and toga virus, e.g., rubella virus and virus responsible for encephalitis and hemorrhagic fever.

Many compounds have antiviral or virustatic activity, i.e., they inhibit the spread of viral infection by inhibiting the replication of virus particles. However, they do not inactivate the virus. Acyclovir, 9-(2-hydroxyethoxymethyl)guanine, an antiviral drug which has recently been cleared by the FDA for use in treating herpes infections in humans, is a virustatic agent, but not a virucide.

Recent research has shown that certain lipophilic compounds inhibit replication of some

enveloped virus in vitro. Sands, Antimicrobial Agents and Chemotherapy, 12, 523-528 (1977), discloses that various fatty acids can inhibit viral replication in bacteriophage, and that at least two modes of fatty acid inhibition can be involved. The first mode involves inactivation of the virus, i.e., virucidal activity. Oleic acid, a monounsaturated C18 fatty acid, was the most effective fatty acid tested for this property, but a C18 acid having two double bonds was essentially inactive. The second method is inhibition of replication, without killing the virus, i.e., anti-viral or virustatic activity. This phenomenon is related to the stage in the infectious cycle in which the fatty acid is added.

Reinhardt et al., J. Virology, 25, 479-485 (1978) disclose that unsaturated fatty acids can inhibit the viral replication of PR4 bacteriophage in vitro. The most effective acids were oleic acid and palmitoleic acid. Arachidonic acid (C20 tetraene) was moderately effective, but less effective than linolenic acid (C18 triene).

Kabara et al., Antimicrobial Agents and Chemotherapy, 2, 23-28 (1972) disclose that certain fatty acids inhibit the growth of gram-positive and gram-negative microorganisms, but no virus species were tested. Some saturated fatty acids had antibacterial activity, mono-unsaturated acids were more effective and dienoic acids were even more active, for C18 fatty acids. However, arachidonic acid was not inhibitory at the concentrations tested.

Sands et al., Antimicrobial Agents and Chemotherapy, 15, 67-73 (1979) disclose antiviral activity in vitro of C14-20 unsaturated alcohols having 1-4 double bonds, the most active being gamma-linolenyl alcohol (6,9,12-octadecatrien-1-ol), while a C20 tetraenyl alcohol had low activity. Lower antiviral activity in vitro was disclosed for saturated alcohols by Snipes et al., Ibid., 11, 98-104 (1977); and Snipes et al., Symp. Pharm. Effects Lipids (AOCS Monograph No. 5), 63-74 (1978).

A need continues to exist for a virucidal agent which is active against enveloped virus and which has very low toxicity, especially one that is a potent topical virucide against herpes virus.

OBJECTS OF THE INVENTION

One object of the present invention is to provide a method for inactivating enveloped virus using an agent of low human cytotoxicity.

Another object of the present invention is to provide a topical virucidal agent which is effective to prevent and/or reduce lesions which accompany herpes infections in animals and humans.

A further object of the present invention is to provide a pharmaceutical composition for use in the foregoing methods.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

SUMMARY OF THE INVENTION

In a method aspect, the present invention provides a method of inactivating enveloped virus, which comprises contacting the situs of said virus or the virus itself with a virucidally

effective amount of a C20-24 linear polyunsaturated acid, aldehyde or primary alcohol having 5-7 double bonds, a pharmaceutically acceptable salt of said acid, or a mixture thereof.

In a preferred method of use aspect, the present invention provides a method of treating lesions associated with a herpes infection in an animal or human subject, which comprises applying to the inflamed area an amount of the foregoing virucidal agent effective for reducing or arresting said lesions.

In a composition of matter aspect, the present invention provides a pharmaceutical composition comprising a virucidally effective amount of the foregoing virucidal agent, and a pharmaceutically acceptable carrier. Preferred such compositions suitable for topical application are also provided.

DETAILED DISCUSSION

The C20-24 linear polyunsaturated acids suitable for use in the present method and composition include eicosapentaenoic acid (EPA), eicosahexaenoic acid, eicosaheptaenoic acid, heneicosapentaneoic acid, heneicosahexaenoic acid, heneicosaheptaenoic acid, docosapentaenoic acid, docosahexaenoic acid (DHA), docosaheptaenoic acid, tricosapentaenoic acid, tricosahexaenoic acid, tricosaheptaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, tetracosaheptaenoic acid and mixtures thereof. Preferred acids are EPA, DHA and mixtures thereof, including both non-conjugated and conjugated double bond isomers. Especially preferred are 5,8,11,14,17-EPA and 4,7,10,13,16,19-DHA and mixtures thereof. It will be appreciated that the foregoing polyunsaturated acids can exist in a variety of geometric isomers, all of which are included in the invention.

The polyunsaturated acids may be employed as pure compounds or mixtures of pure compounds, or they may be employed as concentrates derived from natural vegetable and/or animal sources. Important natural sources of the polyunsaturated acids suitable for use in the invention are fish liver oils and concentrates and/or extracts thereof. It is known that EPA and DHA are present in significant quantities in oils such as cod liver oil, halibut liver oil, tuna liver oil and the like. Saponification and/or solvent extraction of fish liver oils can increase the percentage of free polyunsaturated fatty acids available therefrom by subsequent concentration and/or further extraction.

The C20-24 linear polyunsaturated acids which are not available from natural sources may be synthesized by conventional techniques for producing long-chain polyolefins having either cis or trans double bonds. Such olefin syntheses are disclosed generally in the chapters on olefin synthesis in Harrison et al., "Compendium of Organic Synthetic Methods" (Wiley 1971); and Carruthers, "Some Modern Methods of Organic Synthesis" (Cambridge 1971); and with respect to the closely related carotene systems, in Anand et al., "Art in Organic Synthesis" (Holden-Day 1970), the foregoing being illustrative and not inclusive of all such general references. The carboxyl group can be introduced early, as a protected, e.g., esterified, function, or at the end of the synthetic pathway, by conventional means, as illustrated in the foregoing references. The longer chain acids may also be obtained by homologation of acids having fewer atoms in the carbon chain, by conventional reaction sequences, e.g., Arndt-Eistert homologation, and the like.

The various geometric and position isomers of the polyunsaturated acids and/or the alcohols and aldehydes related thereto may be obtained by one or more conventional separation

techniques well known in the art, e.g., column chromatography, thin layer chromatography, vapor phase chromatography, high performance liquid chromatography, fractional crystallization, and the like. Partial separations, e.g., solvent extraction, molecular distillation, for the purpose of producing more highly active virucidal fractions are also included within the separation methods envisioned for the production of virucidal agents for use in the present method and composition.

The polyunsaturated acids of the invention may be administered in the form of pharmaceutically acceptable addition salts with inorganic or organic bases, where the salts possess comparable and/or otherwise advantageous virucidal activity and which are otherwise physiologically compatible. Suitable inorganic bases to form these salts include, e.g., the hydroxides, carbonates, bicarbonates or alkoxides of the alkali metals or alkaline earth metals, e.g., sodium, potassium, magnesium, calcium and the like. Suitable organic bases include the following amines; lower mono-, di-, and trialkylamines, the alkyl radicals of which contain up to three carbon atoms, e.g., methylamine, dimethylamine, trimethylamine, ethylamine, di- and triethylamine, N-methyl-N-ethylamine, and the like; mono-, di- and trialkanolamines, the alkano radicals of which contain up to three carbon atoms, e.g., mono-, di- and triethanolamine, alkylene-diamines which contain up to six carbon atoms, e.g., hexamethylenediamine; phenylalkylamines, e.g., benzylamine, phenylethylamine and N-methylphenylethylamine; cyclic saturated or unsaturated bases containing up to six carbon atoms, e.g., pyrrolidine, piperidine, morpholine, piperazine and their N-alkyl and N-hydroxyalkyl derivatives, e.g., N-methylmorpholine and N-(2-hydroxyethyl)piperidine, as well as pyridine.

Furthermore, there may be mentioned the corresponding quaternary salts, e.g., the tetraalkyl, e.g., tetramethyl, alkylalkanol, e.g., methyltrimethanol and trimethylmonoethanol, and cyclic ammonium salts, e.g., the N-methylpyridinium, N-methyl-N-(2-hydroxyethyl)morpholinium, N,N-dimethylmorpholinium, N-methyl-N-(2-hydroxyethyl)morpholinium, N,N-dimethylpiperidinium salts, which are characterized by having good water-solubility. In principle, however, there can be used all the ammonium salts which are physiologically compatible.

The transformations to the salts can be carried out by a variety of methods known in the art. For example, in the case of the inorganic salts, it is preferred to dissolve the acid in water containing at least one equivalent amount of a hydroxide, carbonate, or bicarbonate corresponding to the inorganic salt desired. Advantageously, the reaction is performed in a water-miscible, inert organic solent for example, methanol, ethanol, dioxane, and the like in the presence of water. For example, such use of sodium hydroxide, sodium carbonate or sodium bicarbonate gives a solution of the sodium salt. Evaporation of the solution or addition of a water-miscible solvent of a more moderate polarity, e.g., a lower alkanol, e.g., butanol, or a lower alkanone, e.g., ethyl methyl ketone, gives the solid inorganic salt if that form is desired.

To produce an amine salt, the acid is dissolved in a suitable solvent of either moderate or lower polarity, for example, ethanol, methanol, ethyl acetate, diethyl ether and benzene. At least an equivalent amount of the amine corresponding to the desired cation is then added to that solution. If the resulting salt does not precipitate, it can usually be obtained in solid form by addition of a miscible diluent of low polarity, for example, benzene or petroleum ether, or by evaporation. If the amine is relatively volatile, any excess can easily be removed by evaporation. It is preferred to use substantially equivalent amounts of the less volatile amines.

Salts wherein the cation is quaternary ammonium are produced by mixing the acid with an equivalent amount of the corresponding quaternary ammonium hydroxide in water solution, followed by evaporation of the water.

The C20-24 aldehydes and primary alcohols suitable for use in the method and composition of the invention correspond to the acids set forth above, except that the carboxyl group of the acids is replaced by a formyl group or a hydroxymethylene group, respectively. The aldehydes and alcohols similarly exist as various geometric isomers which are included in the scope of this invention.

The primary alcohols and aldehydes may be readily prepared, e.g., by reduction of the corresponding acids, or by other conventional methods. Typically, an acid will be converted to, e.g., a methyl ester, and the ester will be reduced to the corresponding alcohol with a hydride reducing agent, e.g., $LiAlH_4$. The ester, optionally a triglyceride, is converted to the corresponding aldehyde by the method of Gauglitz, Jr. et al., J. Am. Oil Chem. Soc., 37, 425 (1960).

Other conventional techniques for producing an aldehyde or alcohol having the same carbon chain length or having fewer or greater numbers of carbons in the chain are also well known to the art, and are also illustrated inter alia in the aforementioned Harrison et al. reference. The alcohols may be converted to halides, sulfonate esters and the like and used as intermediates for the production of higher homolog alcohols, aldehydes and acids, e.g., by reaction with cyanide, followed by hydrolysis or hydride reduction, or by other conventional synthetic pathways. It may be convenient and/or advantageous to use mixtures of reactants and products from the foregoing synthetic pathways, without further separation, as virucidal agents.

The foregoing examples of virucidal compounds useful in the present invention are intended to be illustrative of the scope of the invention, but not limitative thereof, and the invention includes equivalents of the illustrated compounds that also achieve the disclosed virucidal effects. Contemplated equivalents include mono or polysubstitution of moieties on the polyunsaturated alcohols, aldehydes, acids and salts that will not interfere with their virucidal activity. Suitable such substituents would include halogen atoms, lower alkyl, lower alkoxy, hydroxy and the like, which can be introduced by conventional means.

Isomerization of the double bonds in the polyunsaturated alcohols, aldehydes and acids of the invention may be effected by treatment with various basic catalysts. The aldehyde function should be protected in the form of a base-stable derivative, e.g., an acetal, or should be introduced after isomerization. Typically, a polyunsaturated acid, e.g., a pure acid or a mixture of acids from e.g., a natural marine oil, which usually has an arrangement of double bonds in allylic relation to one another, is treated with a concentrated solution of alkali and heated to promote double bond isomerization. Concentrated aqueous alkali, e.g., 50% KOH, or alkali metal alkoxides in polar solvents, are effective for isomerizing such allylic double bonds. The resultant acids contain double bonds which are partially or fully conjugated, i.e., they form alternating single and double bonds. Accordingly, the progress of the isomerization reaction may be monitored with ultraviolet spectroscopy, which reveals the presence of conjugated double bond systems by the appearance of absorption peaks in the long wavelength end of the ultraviolet spectrum. Isomerization preferably is effected under an inert gas atmosphere to avoid oxidation of the polyene systems.

The polyunsaturated alcohols, aldehydes, acids and salts of the invention, in contrast to the majority of drugs on the market for use in treating viral infections, are unusual in that they have virucidal activity, i.e., they disrupt the virus particles themselves and render them inactive and permanently non-infectious. Is is especially noteworthy that the present compounds are potent topical virucides against enveloped virus, both in vitro and in vivo. They are especially effective for the treatment of lesions produced as a result of herpes virus infections, e.g., oral, genital, ocular and the like. In fact, the topical activity of at least the preferred species against herpes simplex virus type 2 (HSV-2) is at least comparable to, and in some preparations superior to, that of Acyclovir (ACV).

The compounds of the invention appear to prolong the survival time of animals infected with herpes virus, as well as being effective in reducing the formation of lesions. This suggests that the compounds of the invention have systemic activity.

The virucidal properties of the compounds of the invention suggest their use to prevent the spread of infection by enveloped virus, e.g., by incorporating them in a hand cream or lotion for use by physicians both before and after the examination of patients with suspected virus infections. Furthermore, the compounds may be used in fluids used to kill virus on examining tables, instruments, gloves, towels and other surfaces which might come in contact with virus particles during the course of medical examinations. The low toxicity of the compounds of the invention further enhances their attractiveness for such prophylactic use.

Evidence of the efficacy of the virucides of the invention in vitro has been obtained from bioassay using HSV-2, using a standard assay procedure. Serial dilutions of the compounds were tested for their ability to prevent plaque formation by a stock virus suspension. Reduction of plaque titer by test compounds as compared to mock treated controls was indicative of virucidal activity. Minimal inhibitory concentrations (MIC) of the test compounds, defined as the lowest concentration of the test compound capable of producing a 3-log (1,000 fold) reduction in virus titer, were determined. These represent the upper limit for the drug concentration, since dilutions were not carried beyond 1:6400 and in some cases 1:12800. At a dilution of 1:12800, EPA had an MIC of 0.37 .mu.g/ml and DHA had an MIC of 0.47 .mu.g/ml. A purified fraction isolated from cod liver oil hydrolysate had an MIC of 0.42 .mu.g/ml, while a less highly purified hydrolysate fraction had an MIC of 1.00 .mu.g/ml. Cod liver oil itself was inactive.

As evidence of the excellent topical activity of the virucides of the invention against enveloped virus, in vivo tests were carried out in mice and in guinea pigs. These tests were effected using substantially the same procedures as those reported by Pancic et al., Antimicrobial Agents and Chemotherapy, 19, 470-476 (1981). In both studies, DHA was compared with ACV in a controlled study for effectiveness in reducing the occurrence and the severity of lesions resulting from infection by HSV-2 and in reducing mortality resulting from the virus infection. Surprisingly and unexpectedly, a low dose of DHA in an ointment base was highly effective in comparison with ACV in reducing lesions and in reducing mortality rates in mice. In fact, a low dose of DHA in the particular ointment vehicle used for test purposes appeared to have a higher activity than a high dose of the same material in the same vehicle.

While not wishing to be bound by any particular explanation of this phenomenon, it may be related to the action of fluid micelles formed by the fatty acid upon viral envelope proteins, which destabilize the viral membrane and inactivate the virus particle. It is known that lipid

micelle formation and structure is sensitive to lipid concentration and to the composition of the suspending medium. Thus, it is possible that micelles with significantly different properties could be formed at higher concentrations or in different vehicles.

The compounds of this invention can be employed in mixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or wheat starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, and the like.

A preferred mode of application of the virucides of the invention is as a topical agent, either in nonsprayable or sprayable form. Non-sprayable forms can be semi-solid or solid forms comprising a carrier indigenous to topical application and having a dynamic viscosity preferably greater than that of water. Suitable formulations include, but are not limited to, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves and the like. If desired, these may be sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure and the like. Preferred vehicles for non-sprayable topical preparations include ointment bases, e.g., polyethylene glycol-1000 (PEG-1000); conventional ophthalmic vehicles; creams, e.g., HEB cream; and gels, e.g., K-Y gel; as well as petroleum jelly and the like. These topical preparations may also contain emollients, perfumes and/or pigments to enhance their acceptability for various usages.

Also suitable for topical application are sprayable aerosol preparations wherein the virucidal compound, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., a Freon(Chlorofluorocarbon) or environmentally acceptable volatile propellant. Such compositions can be used for application to environmental surfaces, e.g., examining tables, toilet seats and the like, and/or for application to the skin or to mucous membranes. The aerosol or spray preparations can contain solvents, buffers, surfactants, perfumes and/or antioxidants in addition to the virucidal compounds of the invention.

For the preferred topical applications, especially for treatment of humans and animals

suffering from the symptoms of herpes virus infections, it is preferred to use the polyunsaturated acids of the invention, although the unsaturated alcohols and aldehydes are also suitable. Salts of the acids appear to be less effective for topical applications. It will be appreciated that salts can be used to prepare compositions for topical applications, in combination with suitable buffers and/or acids to lower the pH of the final preparation.

The virucides of the invention are generally administered to animals, especially mammals, in virucidally effective amounts, and in dosage unit form. The dose can be administered singly or as divided dosages throughout the day.

In the preferred topical form of administration used to effect the present method, application of a virucidally effective amount of a virucide according to the invention to an infected area, e.g., skin surfaces, mucous membranes, eyes, of an animal or human subject suffering from a viral infection, especially a herpes infection, will generally range from about 0.001 mg to about 1 g per application, depending upon the area to be treated, the severity of the symptoms and the nature of the virucidal agent and the topical vehicle employed. Preferably, dosages in the range 0.01-100 mg will be used. A preferred topical preparation is an ointment wherein about 0.01-50 mg of virucide is used per cc of ointment base, the latter being preferably PEG-1000, and more preferably an ointment containing about 0.1-10 mg/cc of a C20-24 acid according to the invention, preferably DHA and/or EPA, in PEG-1000.

In preparing virucidal compositions according to the present invention, particularly topical preparations using polyunsaturated acids, it is preferable to use acids which are as pure as possible and/or which are substantially free, or have at least a significantly reduced content, of esters, e.g., triglycerides. Thus, where a fish liver oil is used as the source of the polyunsaturated acids, reduction of the natural triglyceride content, e.g., by saponification of the oil and recovery of the saponified acids fraction, will be advantageous.

Alternatively, molecular distillation, solvent extraction, fractional crystallization, liquid chromatography and the like are advantageously used to produce more concentrated and more active fractions. Combinations of the foregoing techniques can be used to achieve still more virucidally effective compositions.

Pharmaceutical preparations wherein substantially pure C20-24 polyunsaturated acids having 5-7 double bonds are used are preferred, especially those which are substantially free of esters, e.g., triglycerides, and most preferably those having substantially pure EPA and/or DHA as substantially the only fatty acids therein. Where a concentrate of polyunsaturated acids is used to prepare the pharmaceutical composition, the content of C20-24 fatty acids having 5-7 double bonds is advantageously at least about 20% by weight, 30% being preferred, and 40%, 50%, 60%, 70%, 80%, 90%, 95% and 99% being even more preferable the higher the percentage of the virucides. Conversely, the lower the triglyceride content, e.g., less than 50%, preferably less than 40%, 30%, 20%, 10%, 5% and most preferably less than 1%, the more preferred is the composition.

It will be understood that formulations and dosages may be varied and may fall outside of the preferred ranges for various uses, e.g., applications to environmental surfaces for prophylactic use and/or veterinary and disinfectant applications.

Aerosols for topical medicinal applications will have similar concentrations and dosages to the creams, lotions and ointments described above, but may have higher or lower

concentrations for other applications, e.g., prophylactic and/or disinfectant use, veterinary applications and the like.

Dosage levels for enteral and/or parenteral administration to achieve systemic activity will generally fall in the range of 0.001 mg-5 g daily, preferably in solid or liquid unit dosages of about 0.01 mg-1 g of virucide together with about 0.1-10 g of a pharmaceutically acceptable carrier. The precise dosages and frequencies of administration will vary in relation to the severity of the clinical symptoms and the nature of the virucide and of the virus species being treated, as well as the nature and size of the subject, in a manner well known to veterinary and clinical practitioners.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLE 1
Preparation of cod Liver Oil Hydrolysate

A 100 ml quantity of medicinal grade cod liver oil (CLO), obtained from Humco Laboratories, was combined with 100 ml of 10% aqueous sodium hydroxide and refluxed for two hours. After cooling, the mixture was acidified with 50% sulfuric acid. The acidified reaction mixture was extracted with ether and the ether layer was washed with water until the wash water was neutral. The ether extract was dried over anhydrous sodium sulfate, filtered, and the ether removed on a rotatory evaporator, to yield 87 ml of a yellow oil. The oil was then combined with an equal volume of 50% potassium hydroxide and heated at reflux for two hours. The resultant reaction mixture was acidified with 50% sulfuric acid and extracted three times with 250 ml portions of ether. The combined ether extracts were washed with water until the wash water was neutral. After drying over anhydrous sodium sulfate, filtering and removing the ether, 56.3 g of CLO hydrolysate (CLOH) was obtained.

An ultraviolet spectrum of the product showed long wavelength absorption, indicating that at least partial conjugation of the double bonds had occurred. The yellow oil obtained prior to the 50% KOH treatment, consisting mainly of unconjugated fatty acids, can also be used as a source of virucide according to the invention, either as such or after further purification, e.g., as shown in Example 2.

It is also possible to obtain a virucidally active concentrate by extracting a fish liver oil, e.g., cod liver oil, with an alcohol, e.g., methanol, and evaporating the alcohol, and optionally saponifying as above and recovering the resultant hydrolysate, which can be further purified, e.g., as in Example 2.

EXAMPLE 2
Fractionation of Cod Liver Oil Hydrolysate

A 1 g sample of the CLOH prepared in Example 1, dissolved in 1 ml of acetonitrile, was chromatographed using reverse phase high performance liquid chromatography (RP-HPLC), using a Chrompack Lichrosorb 10 RP 18 column, 25 cm in length, with 100% acetonitrile mobile phase. The collected fractions were stripped of acetronitrile and weighed. A fraction having a retention time of 2.3 min. and weighing 78.7 mg was produced, and labelled CLOH-

2.3.

A portion of the CLOH-2.3 material weighing 63.0 mg was dissolved in 400 .mu.l of mobile phase and rechromatographed using 90% acetonitrile/10% water. Three major peaks resulted, which were separately collected and the solvent stripped. The amounts obtained after vacuum stripping were: Peak 1, 7.9 mg; Peak 2, 6.2 mg; and Peak 3, 16.0 mg. The peaks were labelled CLOH-2.3-1, CLOH-2.3-2 and CLOH-2.3-3, respectively.

In a separate experiment, it was found that extraction of CLO with methanol, followed by evaporation of the methanol and further extraction of the residual extract with acetonitrile produced a solution which, upon RP-HPLC chromatography, was shown to contain major quantities of materials having the same retention times as the major components in the CLOH-2.3 material. By judicious isolation of RP-HPLC fractions, it was possible to produce a concentrate having very similar chromatographic behavior on RP-HPLC to the CLOH-2.3 material, although the yield of such fractions was substantially lower than the yield of concentrate from fractionation of CLOH.

In a further experiment, enrichment of the CLOH material in the CLOH-2.3 fraction components was effected by extracting a 37.4 g sample of CLOH with three equal volumes of about 15 ml each of acetonitrile. The combined extracts were stripped and weighed, producing 15.1 g of residue, which was redissolved in acetonitrile to a concentration of 1 g/3 ml. RP-HPLC of this material using 100% acetonitrile as the mobile phase showed that the major peak had a retention time of 2.3 minutes, and represented a sustantially greater percentage of the total material in the sample than was the case in the CLOH itself. Accordingly, repetitive injections of this material were made and an additional stock of the CLOH-2.3 fraction was prepared. Further fractionation of the CLOH-2.3 material using 90/10 acetonitrile/water was effected as described above, and material corresponding to CLOH-2.3-3 was collected and vacuum stripped.

EXAMPLE 3

In Vitro Bioassays

Assays were performed using herpes simplex virus type 2 (HSV-2).

Production of Virus Test Materials

Cell Culture. Cell cultures used for the propagation and titration of HSV-2 were the human diploid lung embryonic line MRC-5 and the human malignant epitheloid cell line HEP-2 respectively. Stock monolayer cultures of both cell lines were propagated in Dulbecco's Modified Eagle's medium (DME) supplemented with 10% (V/V) calf serum. Spinner cultures for mass production of HEP-2 cells were grown in Joklik's medium supplemented with 10% (V/V) calf serum and 1% (W/V) pluronic acid. Monolayer cultures of HEP-2 cells for plaque or virucidal assay were seeded into 60 mm dishes in DME supplemented with 10% calf serum and antibiotics. Stock cultures were maintained in antibiotic free medium.

Preparation of HSV-2 Stock and Titration

Herpes simplex virus, type 2 (HSV-2) strain 333 was obtained from Dr. John Hughes of the Dept. of Medical Microbiology, College of Medicine, The Ohio State University. Stocks of

HSV-2 were prepared in the human diploid embryonic lung cell line, MRC-5. Confluent MRC-5 monolayer cultures in T-75 plastic flasks were washed one time with Hank's and Balanced Salt solution (HBSS) and infected with 0.5 ml of HSV-2, strain 333 stock. Virus was adsorbed for 1 hour at 37 DEG C. Then the culture was refed with 15 ml of DME supplemented with 1% (V/V) calf serum. Virus was harvested 48 hours later when cytopathology was complete. Cultures were frozen and thawed rapidly three times to release cell associated virus, clarified by centrifugation at 10,000.times.g for 15 minutes at 4 DEG C., aliquoted into 5 ml lots and frozen at -70 DEG C. One lot was taken for virus titration.

HSV-2 was titrated by plaque assay in HEP-2 cells under a semi-solid methyl cellulose overlay. Tenfold serial dilutions of virus were prepared in HBSS and 0.3 ml aliquots of each dilution inoculated onto triplicate HEP-2 cell monolayers in 60 mm plastic petri dishes. Adsorption of virus was for 1 hour at 37 DEG C. Plates were then overlayed with 5 ml of a 1:1 mixture of 2.times.DME supplemented with 2% (V/V) calf serum and 3% (W/V) methyl cellulose to give a final 1.times.DME supplemented with 1% calf serum and 1.5% methylcellulose. Infected plates were incubated at 37 DEG C. in a humidified 10% CO_2 atmosphere for 48 hours. Virus plaques were visualized by staining with crystal violet and counted under a dissecting microscope. Virus titers were calculated from the plaque numbers by averaging the plaque count and multiplying by 3.3 (0.3 ml plates).

Technique for Virus Assays

The following procedure was employed to assay virucidal activity in various test samples. Compounds were received as a solution in DMSO and were serially diluted in HBSS as described for each experiment. For the test, 1 ml of each dilution was mixed with 1 ml of a stock virus suspension diluted to approximately 9.times.10@3 plaque forming units (P.F.U.)/ml. This test mixture was incubated at 25 DEG C. for 30 minutes, then inoculated onto a cell culture (HEP-2) for plaque assay as described previously. Mock treated (virus plus HBSS) controls were included with each test. Any reduction of plaque titer by test compounds as compared to the mock treated control was indicative of virucidal activity. Minimal inhibitory concentrations (MIC) of test compounds were defined as the lowest concentration of a compound capable of producing a 3-log (1000-fold) reduction in virus titer.

Bioassay of CLOH and Fractionation Products

Samples from RP-HPLC fractionation of the CLOH, produced according to Example 2, as well as purified samples of palmitic, myristic and oleic acids and Vitamin D2, were tested for HSV-2 bioactivity. The results of this bioassay are listed in Table 1. The CLOH-2.3 sample was shown to have an MIC value at least as low as 2.45 .mu.g/ml; the breakpoint was not reached at dilutions of 1:6400. MIC values are shown in Table 2. The CLOH-2.3-3 sample had an MIC of 2.5 .mu.g/ml. Pure oleic acid was not active in this assay, nor were palmitic and myristic acids and Vitamin D2.

Spectral data indicated that the CLOH-2.3-3 material was likely to be a mixture of EPA and DHA. Accordingly, authentic samples of EPA and DHA were obtained from Sigma Chemical Company and their presence was confirmed as major components, together with impurities in the CLOH-2.3-3 fraction. Authentic EPA and DHA and their methyl esters were submitted for bioassay. The samples were prepared with DMSO/HBSS (50:50) to a concentration of 8 mg/ml and assayed at several dilutions. Results of the bioassay are shown in Table 3 and the

MIC values for the samples are shown in Table 4.

TABLE 1
RESULTS OF HSV-2 BIOASSAY OF SELECTED PURIFIED ACIDS, VITAMIN D2 AND RP-HPLC FRACTIONS OF CLO-HYDROLYSATE
Palmitic acid@(a) Vitamin D@(a)
Oleic acid@(a)
plaque plaque plaque
Dilutions
count titer count titer
count titer
1:10 TNTC@(c)
-- TNTC -- 36 1.2 .times. 10@2
1:100 " " TNTC
1:200 " " "
1:400 " " "
1:800 " " "
1:1600
" " "
1:3200
" " "
1:6400
" " "
Myristic@(a)
CLOH-2.3 CLOH-2.3-1
plaque plaque plaque
Dilutions
count titer count titer count titer
1:10 TNTC -- 0 0 0 0
1:100 " 1 3.3 .times. 10@0
0 0
1:200 " 1 3.3 .times. 10@0
2 6.6 .times. 10@0
1:400 " 0 0 14 4.6 .times. 10@1
1:800 " 1 3.3 .times. 10@0
30 9.9 .times. 10@1
1:1600
" 0 0 116 3.8 .times. 10@2
1:3200
" 0 0 TNTC --
1:6400
" 0 0 " --
CLOH-2.3-2 CLOH-2.3-3
plaque plaque
Dilutions
count titer count titer
1:10 0 0 0 0
1:100 0 0 0 0
1:200 0 0 0 0
1:400 1 3.3 .times. 10@0

1 3.3 .times. 10@0
1:800 1 3.3 .times. 10@0
0 0
1:1600 1 3.3 .times.10@0
2 6.6 .times. 10@0
1:3200 2 6.6 .times. 10@0
10 3.3 .times. 10@1
1:6400 4 1.3 .times. 10@1
27 8.9 .times. 10@1
@(a) Control 2.6 .times. 10@4
@(b) Control 1.3 .times. 10@4
@(c) Too numerous to count

TABLE 2
MIC RESULTS FOR HSV-2 BIOASSAY OF SELECTED PURIFIED ACIDS, VITAMIN D2 AND RP-HPLC FRACTIONS OF CLO HYDROLYSATE
Wt. of sample
Dilution showing
MIC value
Sample in mg 3 log reduction
.mu.g/ml
Palmitic acid
5.9 -- --
Vitamin D2
5.0 -- --
Oleic acid
5.0 -- --
Myristic acid
5.9 -- --
CLOH-2.3 15.7 1:6400 2.45
CLOH-2.3-1
7.9 1:200 39.5
CLOH-2.3-2
6.2 1:1600 3.9
CLOH-2.3-3
16.0 1:6400 2.5

TABLE 3
HSV-2 ASSAY RESULTS FOR AUTHENTIC STANDARDS AND RP-HPLC ISOLATED FRACTIONS
(EPA) (DHA) CLOH-2.3-3
DHA--ME EPA--ME CLOH-2.3
plaque plaque plaque plaque plaque plaque
Dilution
count
titer
1:10 0 0 0 0 0 0 95 3.1 .times. 10@2
0 0 0 0
1:100
0.5 1.7 .times. 10@0

0 0 0 0 293 9.7 .times. 10@2
2.5 8.3 .times. 10@0
0 0
1:400
0.5 1.7 .times. 10@0
0 0 0 0 TNTC
TNTC 7.5 2.5 .times. 10@1
0 0
1:800
0.5 1.7 .times. 10@0
0 0 0 0 TNTC
TNTC 13.5
4.5 .times. 10@1
0 0
1:1600
0.5 1.7 .times. 10@0
0 0 0 0 " " 19.5
6.4 .times. 10@1
0 0
1:3200
0.5 1.7 .times. 10@0
0 0 0 0 " " 42.5
1.4 .times. 10@2
0 0
1:6400
0.5 1.7 .times. 10@0
0 0 0.5 1.7 .times. 10
" " 36.5
1.2 .times. 10@2
1 3.3 .times. 10@0
1:12800
0.5 1.7 .times. 10@0
0 0 0 0 " " 66 2.2 .times. 10@2
2.5 8.3 .times. 10@0
control: dilution, 1:100; plaque count, 13.5; titer, 4.5
.times. 10@3
EPA = eicosapentaenoic acid
EPA--ME = eicosapentaenoic acid, methyl ester
DHA = docosahexaenoic acid
DHA--ME = docasahexaenoic acid, methyl ester

TABLE 4
MIC VALUES FOR AUTHENTIC STANDARDS AND RP-HPLC ISOLATED FRACTIONS
Wt. of Sample
Dilution Showing MIC
Sample in mg. 3 log reduction .mu.g/ml
EPA 4.7 1:12800 0.37
DHA 6.0 1:12800 0.47
CLOH-2.3-3

5.4 1:12800 0.42
DHA--ME 5.9 -- --
EPA--ME 5.4 1:10 540
CLOH-2.3 6.4 1:6400 1.00

The in vitro bioassays demonstrated that the polyunsaturated acids, exemplified by EPA and DHA, both in their unconjugated and at least partially conjugated forms, are potent and fast-acting virucides. Separate experiments showed that DHA inhibits more than 98% of the virus within 30 seconds of contact, and better than 99.99% of the virus within 30 minutes of contact.

Comparable results are expected for in vitro activity of the polyunsaturated alcohols, aldehydes and acid salts of the invention.

EXAMPLE 4

In Vivo Bioassays

Using substantially the procedures of Pancic et al., loc. cit., the topical activity of DHA, a representative and preferred virucide for use in the present method, was evaluated in mice and in guinea pigs. Both evaluations included comparative testing against ACV and the mouse tests included a comparison of two different vehicles.

Mouse Bioassay

The antiherpetic activity of DHA and ACV was compared using two evaluation criteria; (1) duration and severity of genital lesions, and (2) increased or decreased survival time.

The experimental groups were:
A. HSV-2 infected DHA treated
(1) Two doses: 1 mg/ml Low and 10 mg/ml High
(2) Two vehicles per dose: ointment and soluble form of the drug
B. HSV-2 infected, Acyclovir treated
(1) One dose of the drug
(2) Two vehicles (as above)
C. HSV-2 infected (infected controls)
(1) Vehicle control (two vehicles)
(2) No treatment
D. Uninfected mice
(1) Vehicle alone
(2) Vehicles and drug (high dose only)
(3) Untreated

This experimental approach provided an indication of whether or not DHA exhibited antiherpetic activity in vivo, as compared to a known active drug Acyclovir. Protocols and treatment regimens are shown below.

Animals

Female Swiss Webster mice were received from Charles River Breeding Laboratories, Inc. at

5 weeks of age and were held in quarantine for two weeks. Pooled sera from selected mice was tested for Pneumonia Virus of Mice, Mouse Hepatitis Virus, Sendai Virus, and Lymphocytic Choriomeningitis Virus. No significant titers were found.

Mice were 7 weeks of age at the beginning of the experiment, were housed 5 per cage, and allowed food and water ad libitum.

HSV-2 Stock Virus Preparation and Titration

HSV-2 strain 333 passaged in MRC-5 cells was inoculated onto confluent HEP-2 monolayers and harvested 48 hours later when 100% of the cells exhibited cytopathology. The cells were disrupted by freezing and thawing three times and the supernatant clarified by centrifuging at 1000.times.g for 10 minutes and by centrifuging again at 8,000.times.g rpm for 10 minutes at 40 DEG C. Virus containing supernatant was aliquoted and frozen at -70 DEG C.

The virus was titrated on confluent HEP-2 monolayers seeded from Spinner culture 24 hours earlier at 2.times.10@6 cells per 60 mm tissue culture dish. Serial ten-fold dilutions of the virus stock were prepared in HBSS and each dilution was inoculated in triplicate onto HEP2 cell monolayers and allowed to adsorb for 60 minutes at 37 DEG C., 10% CO2. Following adsorption the plates were overlayed with a 3% methylcellulose overlay in Dulbecco's Modified Eagle's Medium +20% calf serum and incubated at 37 DEG C., 10% CO2 for 48 hours and subsequently stained with crystal violet. Plaques were counted with the aid of a microscope, and the titer of the stock virus preparation was 4.4.times.10@8 p.f.u./ml.

Virus Infection of Mice

Pre-Treatment with 0.1N NaOH. 24 hours before inoculation with HSV-2 virus, mice were washed intravaginally with sterile 0.1N NaOH to irritate the vaginal tissue. 0.15 ml 0.1N NaOH was introduced intravaginally with a sterile eye dropper and the area flushed three times. Two hours prior to virus inoculation mice were swabbed intravaginally with 0.1N NaOH, using a sterile cotton swab.

Virus Inoculation. An aliquot of HSV-2 suspension in HBSS was thawed quickly and diluted 1:10 in HBSS. 0.020 ml of the diluted virus suspension was introduced intravaginally using an Eppendorf pipet with separate, sterile Eppendorf pipet tips for each mouse. The inoculation was done in a biohazard hood. Each infected mouse received 1.times.10@7 p.f.u. of HSV-2.

Drug Preparation

Vehicles. A 70% dimethyl sulfoxide (DMSO)--30% HBSS solution or polyethylene glycol 1000 (PEG) served as carriers for the Acyclovir or DHA and were also administered alone, as controls. The DMSO-HBSS vehicle was selected based on the observed (visually) solubility of DHA in various DMSO-HBSS solutions. 1 mg DHA was soluble in 1 ml of 70% DMSO-30% HBSS.

Acyclovir. A 5% weight/volume mixture of unionized Acyclovir or the sodium salt of Acyclovir was prepared in 70% DMSO-30% HBSS and in PEG 1000. The PEG 1000 was warmed to facilitate uniform suspension of the drugs. The use of the sodium salt of Acyclovir in either carrier required the addition of 1N HCL to neutralize the mixtures.

4,7,10,13,16,19 Docosahexaenoic Acid (DHA). A weight/volume mixture of 1 mg DHA per ml carrier or 10 mg per ml carrier constitute the low and high doses of test drug prepared. The PEG 1000 was warmed to facilitate mixing.

Drug Administration and Animal Observations

Control and infected mice were treated in a biohazard hood with carrier plus drug or carrier alone twice daily Monday through Friday and once daily Saturdays and Sundays. The treatment regimen was initiated three hours post HSV-2 intravaginal inoculation and was continued for 14 days thereafter. DMSO-HBSS alone or DMSO-HBSS plus drug was delivered at 0.15 to 0.2 ml per mouse, using separate, sterile eye droppers. PEG 1000 alone or PEG 1000 plus drug was warmed and delivered at approximately 0.15 ml per mouse, using separate, sterile swabs.

Infected and control mice were allowed food and water ad libitum and were observed once daily for clinical signs of virus infection for 14-21 days following HSV-2 innoculation. Vaginal HSV-2 infection was scored according to the following description. A score of 0 indicated no clinical signs of vaginal infection. A score of.±.indicated slight perivaginal redness. A score of 1 indicated perivaginal redness and swelling of 1-2 mm. A score of 2 indicated perivaginal redness and swelling of 2-3 mm. A score of 3 indicated perivaginal and perianal redness and swelling of 3-4 mm. A score of 4 indicated perivaginal and perianal redness and swelling of 4 mm or more, with exudate.

The results are summarized in Tables 5 and 6. It is seen that DHA showed effective virucidal activity against HSV-2, especially the low dose ointment preparation. The validity of this test procedure is shown by the fact that ACV was effective in minimizing the clinical signs of infection in either carrier vehicle and in achieving a survival rate of 100% in both groups within the observed 14 day period. It should also be noted that neither carrier or any of the preparations showed signs of toxicity in the tested animals.

Guinea Pig Bioassay

A blind comparative test was carried out on guinea pigs using coded substances labeled A through D. The testers were told only that one of the four substances was ACV, that the other three coded samples were the same material, in concentrations of 0.1, 1.0 and 10 mg/ml, and that all four samples were formulated in a polyethylene glycol 1000 (PEG-1000) vehicle. A separate sample of the PEG-1000 was also submitted to serve as a placebo for treating virus control animals. The materials and experimental protocol is shown below.

Animals. Female Hartley strain albino guinea pigs weighing about 450-500 g were used. The animals were quarantined 24 hr prior to use in this study, and maintained 5 to a 32".times.32".times.9" stainless steel cage on Wayne guinea pig diet and water ad libitum.

Virus. Strain E194 of herpes virus type 2 was used. The virus was initially obtained from Dr. M. Fiala, Harbor General Hospital, (Torrance, CA), and an MA-104 culture pool was prepared and pretitered in guinea pigs. The virus was held at -90 DEG C. until used.

TABLE 5
IN VIVO MOUSE BIOASSAY TREATMENT
ACYCLOVIR

High DHA
Low DHA
NO TREATMENT VEHICLE*
(5% wt/vol)
(10 mg/ml)
(1 mg/ml)
RESULTS (control) PEG DMSO
PEG DMSO
PEG
DMSO
PEG
DMSO
Animals/Group
10 10 10 10 10 10 10 10 10
Infected,
6 5 8 4 3 5 4 1 4
Day 14
# of Deaths,
4 3 5 0 0 3 2 0 2
Day 14
Max. Lesion
+4 +4 +4 .±.
Score** +3 +3 +1
*PEG = Polyethylene Glycol
DMSO = Dimethylsulfoxide
**Lesion Scoring System
##STR1##

TABLE 6
IN VIVO MOUSE BIOASSAY
Maximum %
Mean Day % Morbidity
Group of Death Mortality
(Day)
DMSO, Control 9.8 40 80 (8)
DMSO & High DHA
8.5 20 40 (7)
DMSO & Low DHA 11.7 30 40 (7)
Ointment, Control
10.3 30 50 (7)
Ointment & High DHA
11.7 30 50 (7)
Ointment & Low DHA
>14 0 10 (6)
DMSO & Acyclovir
>14 0 30 (7)
Ointment & Acyclovir
>14 0 40 (7)
HSV-2 Control 9.5 40 60 (8)

Drugs. The substances tested consisted of four bottles labelled "A", "B", "C", and "D" with no identifying key. The samples were: A, 0.1 mg/ml DHA (0.003 mmol/ml); B, 5% w/w ACV (0.22 mmol/ml); C, 1 mg/ml DHA (0.03 mmol/ml); and D, 10 mg/ml DHA (0.3 mmol/mg). Each substance, at room temperature, had a hard wax consistency, so was warmed to 45 DEG C. in a water bath and gently mixed immediately prior to use in treatment. All were treated as light-sensitive compounds.

Experimental Protocol. The guinea pigs were infected by applying a virus-soaked swab intravaginally, with agitation, for 20 seconds. Toxicity control animals were similar pretreated using swabs soaked in sterile Puck's balanced salt solution. Treatment began 20 hr later, with the compound or placebo applied topically intravaginally, perivaginally, and perianally using cotton swabs soaked in the respective substance. Treatment continued three times daily (8 a.m., noon, 4 p.m.) for 7 days. Ten infected animals were used for each coded substance, with twenty used for virus controls. Five sham-infected animals were concomitantly treated with each coded substance to serve as toxicity controls. Two guinea pigs were held separately to serve as normal untreated controls.

Each animal was observed daily for survival for a total of 28 days. On days 5 through 8 post-virus inoculation, the genital area was carefully examined and signs of irritation in the toxicity controls and lesion severity in injected animals was scored on a 0 to 4 scale using the same scale as in the mouse bioassay. The results were scored as average daily lesion (ADL) scores for each group, and as mean vaginal lesion (MVL) scores, calculated as the mean of the ADL scores for days 5-8. The maximum mean score for the toxicity control animals was also determined.

On day 6 prior to the 8 a.m. treatment, intravaginal and perivaginal areas of each infected guinea pig were uniformly swabbed with sterile cotton swabs. The swab for each animal was placed in 1.0 ml of sterile Eagles minimum essential medium and immediately frozen at -90 DEG C.; several days later all were thawed and each swab-containing sample vortexed for 15 seconds and then the sample was diluted through a series of 10-fold dilutions in sterile medium. Each dilution was assayed for virus in triplicate by adding 0.1 ml to an established monolayer of MA-104 cells in 96-well disposable plastic microplates. The plates were sealed, incubated at 72 hr at 37 DEG C., and virus-induced cytopathic effect noted microscopically.

Data Analysis. Increases in survivors were analyzed using chi squareanalysis with Yate's correction. Mean survival times (MST) of animals dying on or before day 29 were determined for each group, and evaluated using the t test. Titers of virus recovered from vaginal areas were expressed as 50% cell culture infectious dosages calculated using the Reed-Muench procedure, and titer decreases evaluated by t test.

The results are summarized in Table 7. This experiment used a high level of virus to infect the animals, which was selected to induce eventual deaths in all of the infected animals. As a consequence, the total survival and mean survival time data were of considerably less significance than the effect on the severity of lesions and on the vaginal virus titer. In this experiment, neither ACV nor the lowest dosage of DHA were able to achieve a statistically significant reduction in lesion scores. Animals receiving the higher dosages of DHA of samples "C" and "D" had statistically significant reductions in lesion scores. Significant decreases in vaginal virus titer were seen in all the treated groups compared to the placebo treated group.

TABLE 7
COMPARATIVE BIOASSAY WITH TOPICAL ADMINISTRATION
Infected, Treated
Toxicity Controls MVL MVL MVL MVL
Max. Irrit. MST MVL Scores
Vag. Virus
Treatment Group
Surv/Total
Score Surv/Total
(days)
Days 5-8
Day 5
Day 6
Day 7
Day
Titer
"A" 5/5 0.0 6/10 12.3 3.2 2.4 3.0 3.5 3.8 10@2.3 **
"B" 5/5 0.0 5/10 11.6 2.8 1.8 2.3*
3.4 3.3 10@2.3 **
"C" 5/5 0.0 4/10 13.3 2.4* 1.7 2.3*
2.8 3.1 10@2.4 **
"D" 5/5 0.0 8/10 16.5 2.4* 1.5* 2.1*
3.0 3.1 10@3.1 *
Placebo 13/20 14.3 2.8 2.1 2.7 3.0 3.2 10@3.7
Normals 0.0 2/2 >21.0
0.0 0.0 0.0 0.0 0.0
*P < 0.05
**P < 0.001

No topical irritation was observed in any drug-treated group.

EXAMPLE 5
Ointment Formulation

An ointment suitable for administration according to the method of the invention is prepared as follows. The ointment is designed for topical administration to skin and mucus membrane surfaces which are infected with enveloped virus. The ointment should be gently rubbed on the affected area until it disappears. The frequency of administration and variations in dosage will depend on the clinical indications.

DHA 1 g
PEG-1000 1,000 ml

The PEG-1000 is warmed to about 45 DEG C. in a water bath until it melts and liquifies. The DHA is then added and blended to achieve homogeniety. Optionally, other ingredients may be added to modify the composition, e.g., stabilizers, emollients and the like.

EXAMPLE 6
IM Injectable Formulation

A preparation suitable for intramuscular injection according to the method of the invention as prepared as follows.
DHA 10 mg
Butylated hydroxyanisole
0.01% w/v
Butylated hydroxytoluene
0.01% w/v
Peanut Oil or Sesame Oil
1.0 ml
sufficient to make

The ingredients are blended, the blended ingredients are placed in an ampoule, which is sterilized and sealed.

EXAMPLE 7
Powder Formulation

A powder for use on areas affected by virus infections and suitable for administration according to the method of the invention is prepared as follows:

DHA 5% w/w Silicon dioxide, anhydrous 0.5% w/w Corn starch, lactose, fine powder- 1 kg each, with the total sufficient to make

The ingredients are mixed and blended to form a powder composition suitable for topical application according to the invention. It will be understood that other ingredients, e.g., perfumes and/or preservatives, may be incorporated in the composition.

EXAMPLE 8
Disinfectant Spray Formulation

A spray which may be applied to the hands, the skin and/or mucus membranes, and which is also suitable for disinfectant use on instruments, examining tables, toilet seats and other surfaces upon which virus may be deposited, is prepared as follows:

DHA 25 g
Butylated hydroxyanisole 4.0 mg
Poloxamer 235 (poly(oxypropylene)-25.0 g
poly(oxyethylene) copolymer surfactant, Av. M.W. 46,000)
Benzyl alcohol 4.7 ml
Isotonic saline 500.0 ml

300 ml of isotonic saline are combined with the poloxamer 235 and thoroughly mixed, after which the DHA, the butylated hydroxyanisole and the benzyl alcohol are added and thoroughly mixed. Additional isotonic saline is added to make up the volume to 500 ml. It will be understood that other ingredients may be added to this formulation and the amount of virucide may be varied as a function of the intended use to which the spray is put. The spray may be packaged in pump dispenser bottles or in a spray can together with an environmentally acceptable propellant, under pressure.

EXAMPLE 9

Tablet Formulation

A tablet suitable for administration according to the method of the invention is prepared as follows. Each dosage unit is designed for administration to a patient weighting about 80 kg. The frequency of administration of the illustrated tablets will depend upon the type of virus infection being treated, the severity of the symptoms and the nature of the subject being treated.

EPA 200 g
Wheat starch 26 g
Lactose 76 g
Magnesium stearate 6 g

A granulation obtained upon mixing lactose with a portion of the starch and granulated starch paste made from the remainder of the starch is dried, screened and mixed with the EPA and the magnesium stearate. The mixture is compressed into 1000 tablets weighing about 308 mg each. It will be understood that a dragee or a capsule may be used in place of a tablet, and it may be prepared by conventional techniques.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions o of this invention for those used in the preceding examples.

Method and preparations for relieving pain and producing analgesia US3898325

A method of treating a host for inducing relief of pain or anesthesia which comprises administering histamine, its salts, or an agent inducing histamine release, and a dispersing agent such as hyaluronidase, at the place of the painful area or at the place indicated for acupuncture for the painful site.

BACKGROUND OF THE INVENTION

1. Field of the Invention:

This invention relates to a method and preparations for relieving pain and producing analgesia.

2. Description of the Prior Art:

A great deal of research has been performed on the effect of histamine and related compounds, both in vivo and in vitro. The literature on this subject is so vast and conflicting that it is simply not practical to set forth any meaningful discussion on the subject. For example, Rosenthal et al. have reported in Am. J. Physiol. 155, 186- 90 (1948) that painful sensations are produced by the injection of histamine and in the Proc. Soc. Ecptl. Biol. Med. 74, 167- 70 (1950) that histamine introduced into the superficial layers of human skin causes an immediate as well as latent painful sensation. Jacob et al., Am. inst. Pasteur 81, 128- 92 (1951), have reported that histamine diHCl given to rats subcutaneously or intraperitoneally

for 6 to 30 days decreased their sensitivity to thermal induced pain, but which returned after cessation of treatment.

Similarly a great deal of research has been performed with spreading agents such as the hyaluronidase enzyme. Hyaluronidase has been used alone and in combination with various drugs. The use of hyaluronidase and histamine has also been studied. For example, it has been reported by Seelich et al., Nature 168, 1125 (1951), that histamine does not neutralize heparin inhibitian of hyaluronidase and by Mathies et al., in Z. ges. exptel. Med. 133, 32- 37 (1960), that the inhibitary action of phenylbutazone against hyaluronidase could be blocked by the simultaneous administration of an antihistaminic agent. A vast amount of additional publications exist, both with respect to histamine and hyaluronidase, none of which, to applicant's knowledge, disclose or teach the invention disclosed and claimed herein.

SUMMARY OF THE INVENTION

It has been found that administering histamine, its salts, compounds inducing histamine release, and dispersing agent such as hyaluronidase, or derivatives of histamine, having substantially the same pharmacological activity of histamine, directly to the painful area or at the sites indicated for acupuncture for that painful area, will relieve the pain and produce analgesia at the painful area.

The term, histamine, is used herein in its generic sense, to include histamine, its non-toxic salts, compounds which induce histamine release in the body and histamine derivatives which produce a similar pharmacological activity within the body.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Histamine, its non-toxic salts, compounds inducing histamine release, and histamine derivatives having a similar pharmacological activity in the body are well known and their properties and pharmacological action well documented in the literature. All such compounds are operable so long as they are capable of depositing directly or indirectly a sufficient amount of histamine in combination with hyaluronidase to induce analgesia or relief of pain. The main object is to impart by injection to the painful area or at the acupuncture sites histamine or a related compound having the same pharmacological action as histamine in combination with hyaluronidase. Whether this is accomplished by use of histamine itself or its non-toxic salts, or in any other manner, is not material and is to be considered within the present invention.

The dispersing or spreading factor can be a hyaluronidase of different origins, for example, from honey-bee venom, snake venom, etc. z-N-acetylglucosamidase has been found to be most efficient. These dispersing agents or factors and the methods by which they may be obtained are well known in the art.

The pain relieving or analgesic compositions of this invention can be prepared for injection by placing the histamine compound and hyaluronidase in a suitable medium, such as water, saline solution, isotonic solution, etc., with proper sterilization, as will be apparent to those skilled in the art.

The histamine compound and the hyaluronidase can be separately injected into the painful area or the acupuncture site for that painful area, but it is, of course, more convenient to

combine the histamine compound and the hyaluronidase in a convenient solution.

The concentration of the hyaluronidase enzyme, because of its variable activity, depending upon its source and other well known factors, is given in units as set by the National Formulary. The unit concentration is given on each package as units NF (TR) per volume of weight.

The amount of histamine and/or hyaluronidase that can be injected will depend upon the particular patient being treated, the extent of the painful area, and the degree of pain. A sufficient amount of the histamine compound and the hyaluronidase should, of course, be injected to overcome the pain as will be apparent to any physician.

With respect to the histamine compound, the minimum amount has so far been determined to be about 0.01 mg., and with respect to the hyaluronidase about 10 units NF (TR), [hereinafter referred to as units or units per ml.]. Lower amounts could be used if conditions so indicate.

The maximum amount of the histamine compound that can be used will depend somewhat upon the patient and his tolerance to "flushes" due to histamine reaction. Generally, amounts up to 0.5 mg. can be tolerated.

The maximum amount of hyaluronidase that can be used will again depend upon the particular patient to be treated as well as the amount of histamine being injected. Investigation to date indicated that one would not require more than 50 units of hyalurondase.

Thus, the preparations of this invention can be prepared in such a manner so that the patient can receive between about 0.01 mg. and 0.05 mg. of histamine and between about 10 and about 50 units of hyaluronidase. Experiments to date have shown that an injection of 0.02 mg. of histamine and 10 units of hyaluronidase is advantageous.

The solutions can be made up in varying concentrations and the total volume injected will, of course, depend upon the concentration of the solution. For example, if a solution is made up to contain 0.02 mg. of histamine per ml. and 10 units of hyaluronidase per ml., an injection of 1 ml. of this solution into the painful area or the acupuncture site should be sufficient.

The solutions can be injected into the painful area by any means sufficient to relieve the pain, such as, subcataneously, or deeper into the tissues, periaticular, or even in the articulations, or in the sites used for acupuncture. Depending upon the area of pain, one injection may suffice or, if the painful area is larger, the composition or preparation may be injected into a plurality of places in the painful area, such as in Example 1, set forth below. Such a procedure is referred to herein as infiltration of the painful area. For example, in bursitis, at times, no burt can be located and in which case the entire painful area, the shoulder for example, may be infiltrated, injecting the total amount of desired histamine and hyaluronidase into the shoulder at a plurality of sites. In this case it may be, at times, desirable to have a more diluted solution, so that a larger area can be infiltrated and, at the same time, decrease the chance of any histamine reaction by the patient. Thus, the two main defects of the method, the missing of the painful spots and the "flushes" due to histaminic action, are controlled by this infiltration technique using more diluted solutions of histamine.

As previously mentioned the method of this invention can also be practiced by injecting the preparations at the acupuncture sites for the areas in which it is desired to relieve pain or

produce analgesia. These sites are well known and are described for example, in ACUPUNCTURE THERAPY, CURRENT CHINESE PRACTICE, by T. Tan, Y-C. Tan and Veith, Temple University Press, Philadelphia, 1973.

One advantage of this acupuncture technique is the fact that the results are not the function of the capacity of the individual to respond to the needle insertion with the liberation of histamine, and the use of this invention results in increased responses in the patient. Another advantage is the fact that the injection of the preparations, according to this invention, will affect the entire area or acupuncture site rather than just a single point, and the chances of having the necessary acupuncture site influenced is thus highly increased. The preparations of this invention can thus be used for the treatment of different conditions for which acupuncture is presently used, such as for the induction of anesthesia for surgical interventions.

It has also been noted that together with the suppression of the pain, the evolution of lesions also appears to be influenced.

In all cases where a patient is treated, as a precautionary measure, an anthistamine injection or adrenaline for injection was kept available in case of hypersensitivity to histamine. It is interesting to note, however, that in over 100 cases treated so far there was no need to use either the histaminic preparation or adrenaline, even in a case (Example 10) of the patient who had a history of servere histamininc reactions.

The following examples illustrate the practise of the invention:

EXAMPLE 1

A 60 year old male with severe pain and totally immobilized by a "frozen shoulder" due to bursitis. The condition had gotten progressively worse over the last two months and did not respond to various treatments. From a solution containing 0.2 mg. of histamine phosphate and 10 units of hyaluronidase per ml., 2 ml. divided in 4 injections were injected in the painful spots. The pain disappeared in less than 6 minutes, with recovery of movement. Seen after 2 weeks, the good effects were persistent.

EXAMPLE 2

A 58 year old female with severe arthritis pain in the coccidial region for several months. The pain could not be controlled by various treatments. From a solution containing 0.05 mg. of histamine phosphate and 10 units of hyaluronidase per ml. - 1 ml. was injected in the painful area. The pain disappeared in 4 minutes and remained as such at an examination one month later.

EXAMPLE 3

A 50 year old male with pain due to a sciatica of the left leg, not responding to treatments for the last month. A total of 3 ml. of a preparation containing 0.05 mg. of histamine and 10 units of hyaluronidase per ml. was injected deep subcutaneously in 5 different painful spots. The pain disappeared and remained as such after 2 months.

EXAMPLE 4

A 38 year old female with lower abdominal pains due to an inflamation of both ovaries, lasting for months. (Three) 3 ml. of a solution containing 0.04 mg. per ml. of histamine phosphate and 10 units of hyaluronidase per ml. were injected subcutaneously in the right side painful area. The pain disappeared in 5 minutes and did not reappear. The pain in the left side was not influenced and was treated 4 days later with the same dose. The patient remained without pain for at least 6 weeks.

EXAMPLE 5

A 70 year old female with pains in the left knee, and unable to localize the pain otherwise than the entire anterior area of the knee. A subcutaneous infiltration of this region with 10 ml. of a solution containing 0.01 mg. per ml. of histamine phosphate and 10 units of hyaluronidase per ml. was followed by the disappearance and without recurrence of the pain after 12 days.

EXAMPLE 6

A 62 year old female with severe pain in the left sacroiliac articulation, persisting for months. A subcataneous injection of 0.5 ml. of a solution containing 0.2 mg. per ml. of histamine and 10 units of hyaluronidase per ml. at the painful area did not completely suppress the pain after 15 minutes. A same amount of the solution injected deep into the articulation fully controlled the pain, with the effect still persisting after 3 weeks.

EXAMPLE 7

A 50 year old male with a cancer of the spine, at the 10-12 D and 1 D for which a decompressioin intervention was performed. The patient had very severe pain, on both sides of the lesion, only insufficiently controlled by opiates. From a solution containing 0.2 mg. of histamine phosphate per ml. and 10 units of hyaluronidase per ml., several injections totalling 1.5 ml. were made only at the right side of the spine. The pain disappeared after 6 minutes and still did not reappear after one week, while the pain persisted unchanged in the left side of the spine. The same injection in left side had the same good effect.

EXAMPLE 8

A 40 year old male with severe backache. The painful area was injected with 2 ml. of a 0.1 percent by weight solution of compound 48/80 and 10 units of hyaluronidase per ml. in a saline (sterilized by filtration). The pain was controlled in about 15 minutes and the effect still persisted after one week.

EXAMPLE 9

A 63 year old male with pains in the elbow after playing tennis. The pain persisted for weeks, in spite of treatment. A local infiltration of 7.5 ml. of a solution containing 0.02 mg. per ml. of histamine and 20 units of hyaluronidase per ml. was injected locally. The pain disappeared in 5 minutes. The patient did not have any flushing sensation.

EXAMPLE 10

A 30 year old male with a very painful shoulder of osteoarthritic nature. An infiltration of the

entire painful area, with 20 ml. of a solution containing 0.1 mg. of histamine per ml. and 10 units of hyaluronidase was made. The pain was controlled in less than 10 minutes. The patient remained without pain 6 weeks after the infiltration. The patient, who had a severe histaminic reaction because of a prior use of histamine for a gastric test, with headache, itching and vision troubles did not have any adverse reaction after treatment.

As can be seen from the above examples, abdominal pain from ovary inflammation and gallbladder colics wee controlled by deep subcataneous injections in the painful areas. Even cancer pains responded well to the injections. Good results were obtained for different neuralgias, such as sciatica, tic douloureux, post Zonz Zoster neuralgia, with injections made "locus dolendi" (painful spots). The effects were good also in fractures and especially in residual pains after trauma. In general, with only very few exemptions, the results in more than 100 cases treated are exceptionally good, with not only the pain immediately controlled and with functional recovery, but with the results lasting for a long period of time, weeks or even months after the injections. The pain entirely disappears in less than about 15 minutes in most cases. In some cases the pain was felt after one or two days, but in these cases the pain was felt in areas other than those injected. No local numbness was noted.

Method for eliminating or reducing the desire for smoking US4416869

The invention relates to a method of preventing or reducing the desire for smoking tobacco in humans by the internal administration of a composition produced by heating certain allylically unsaturated compounds sufficient to substantially increase the peroxide titer. The incorporation of sulfur in the composition during the heating has been found to be particularly advantageous.

BACKGROUND OF THE INVENTION

Sulfurized polyunsaturated oils, or sulfurized oils, are disclosed in a book entitled RESEARCH IN PHYSIOPATHOLOGY AS BASIS OF GUIDED CHEMOTHERAPY by Emanual Revici, M.D., published by D. Van Nostrand Company, Inc., 1961, pages 334 and 335. A method of preparing sulfurized polyunsaturated oils referred to in the book as hydropersulfides is set forth in Note 7, page 711 of the book. This book does not disclose the use of the sulfurized compounds for preventing or reducing the desire for smoking tobacco claimed herein.

SUMMARY OF THE INVENTION

The invention relates to a method of eliminating or reducing the desire for smoking tobacco in humans by the internal administration of a composition produced by heating certain allylically unsaturated compounds in the presence of oxygen sufficient to substantially increase the peroxide titer. The incorporation of sulfur into the composition during or before the heating of the compositions has been found to be particularly advantageous and represents the most effective composition found to date. The compositions can be administered to the patient by the various accepted methods such as by injection or preferably orally in capsule form.

DETAILED DESCRIPTION OF THE INVENTION

It is desirable to have a method for treating or aiding in the treatment of the tobacco habit or addiction in a human by controlling the craving for tobacco and/or by controlling withdrawal symptoms.

This invention relates to such methods of treatment involving the internal administration to a human host of a composition produced by oxidizing a fatty acid or fatty ester, for example, by bubbling air through the reaction mixture, structurally characterized by allylic unsaturation alone. The fatty acid or ester advantageously includes elemental sulfur and/or a conventional free radical initiator such as tertiarybutyl peroxide during the heating step.

The allylically unsaturated compound is preferably a naturally occurring fatty ester such as an animal, vegetable, or fish oil. Sesame oil is a vegetable oil consisting largely of triglycerides and is the most advantageous composition found to date in the practice of this invention.

The composition utilized preferably should contain a significant percentage of allylic moieties (to render the compositions useful according to the invention) indicated by the following partial structures
--CH.dbd.CH--CH2 --CH.dbd.CH--

and/or
--CH.dbd.CH--CH.dbd.CH--CH2

As indicated, the unsaturation can be conjugated or nonconjugated but the composition must contain allylic methylene hydrogen.

Such compositions, as the case may be, should be oxidized or heated in the presence of oxygen at a temperature in the range between about 110 DEG C. and about 150 DEG C. The oxygen can be obtained by merely heating the composition open to the atmosphere but preferably and advantageously, the source of oxygen is a gas such as air injected into a heated oil such as sesame oil. The injected air also serves as a source of agitation.

As previously stated it is most advantageous to add elemental sulfur such as sublimed, precipitated, or washed sulfur to the compositions so that the sulfur is present with oxygen during at least a portion of the heating period and the sulfur incorporated into the composition. Additionally, a previous batch of the oxidized oil with or without sulfur or tert-butyl peroxide may advantageously be present during at least a portion of the heating period.

If sulfur is added to the selected composition, for example, sesame oil, the temperature should be maintained at an upper limit within the range of about 120 DEG C. to about 130 DEG C., and preferably 125 DEG C. and 127 DEG C. These temperature limitations are based on a heating time of about one-half hour. The temperatures can be altered within limits depending on the time of heating. For example, the temperature can be 129 DEG-130 DEG C. if the time is shorter or even at 140 DEG C. for very short period of time. High temperatures for a prolonged period of time tend to degrade the composition and should thus be avoided.

If sulfur is not present during the heating period, the temperature should be maintained in the range between about 110 DEG C. and about 150 DEG C., and preferably in the range

between about 120 DEG C. and about 140 DEG C.

The heat treatment is conducted for a period of from about 15 minutes to about two hours. If sulfur is present, optimal results are obtained if the heat treatment is conducted for a period of time between about 30 minutes to about 1 hour. If a free radical initiator is present, or if a selected composition inherently contains a significant amount of initiator, the heat treatment period may be conducted for a relatively shorter period of time.

The precise nature of the composition which results from the above-described treatment or the identity of the effective component or components is not presently known to the applicant. However, while applicant does not wish his invention limited by the following theory or fact, or mixed theory and fact as the case may be, certain evidence in available which indicates that an efficacious composition for the preventing or reducing the desire for tobacco in a human can be produced according to this invention.

In particular, it appears that a correlation exists between a composition useful for the subject purpose and its presumed peroxide or hydroperoxide content. By adhering to the process according to this invention, it has been found that efficacious compositions are produced which yield a significant peroxide titer when monitored by conventional iodometric analysis, the results being expressed, for example, in terms of micro-equivalents per gram. By significant peroxide titer is meant a value obtained which is greater than that which inherently may be present in the initial untreated compound.

In the case of triglycerides which contain the allylic type unsaturation as described above, the resulting oxidized species is thought to be a hydroperoxide represented by the following partial structure ##STR1## as interpreted via UV spectroscopic analysis, inter alia.

Whatever the nature of the oxidized species, it appears amenable to monitoring by conventional iodometric analysis with or without the addition of sulfur.

Although it appears that the activity of the composition is coincident with the presence of peroxides or hydroperoxides, the efficacious agent need not necessarily be directly derived from these classes. It may in fact be those species derived from radicals resulting from decomposition of compounds of, for example, triglyceride oils or sulfur including olefinic polymerization products and/or lower molecular weight decomposition products of the oils or additional products with sulfur such as sulfides, disulfides, hydropersulfides, etc.

With regard to a preferred embodiment, it appears that the presence of elemental sulfur (approximately 1% by weight based on sesame seed oil) during the oxidation of sesame oil increase the amounts of oxidation products (conjugated hydroperoxides, diene, triene, unsaturated carbonyl) and that this increase appears optimal near 127 DEG C. as evidenced by UV spectroscopic analysis studies. In the absence of sulfur, it appears that the region near 127 DEG C. is optimal for the production of oxidation products.

As mentioned above, it appears that the most effective compositions are those which have a relatively high peroxide titer. Comparisons of a preferred composition, namely sesame seed oil oxidized or treated with air in the presence of sulfur, with other triglycerides, or triglyceride containing oils, including corn oil, cottonseed oil, and triolein with regard to their respective peroxide titers indicates a trend in peroxide levels concordant with observed bioactivity in those having an addiction to tobacco. Such trend of bioactivity agrees in

general with the results of a peroxide analysis involving the above-identified oils in their untreated state and when oxidized in the presence of elemental sulfur under similar conditions as follows:

PEROXIDE ANALYSIS (meq/kg.)
Oil Used "A" "B" .DELTA. =
"B - A"
(Peroxide
Oil Saturated
Oil Treated* Difference In
Analysis)
With Sulfur
with Sulfur and Air
Peroxide
Sesame Seed
18.8 35.7 16.9
(10.2)
Corn 11.3 14.9 3.6
(6.8)
Cottonseed
10.9 10.2 -0.7**
(7.3)
Olive 12.4 13.8 1.4
(5.9)
Triolein 8.6 8.5 -0.1**
(7.2)
*Heated at 127 DEG C. for 0.50 hrs. with 90 l/min. air addition and rapid mechanical stirring and containing 1.0% elemental sulfur by weight.
**Within experimental error.

It is thought that a lower bioactivity and a lower peroxide titer of cottonseed oil is due to the presence of natural anti-oxidants. The elimination of the anti-oxidants from oils such as corn and cottonseed oil or the use of the relatively pure allylically unsaturated compounds or mixtures thereof will produce a substantially increased peroxide titer when treated according to this invention. Triolein contains only oleic acid moieties which are characterized by the allylically unsaturated group --CH.dbd.CH--CH2 -- and hence is quite difficult to oxidize,* particularly when compared to the preferred sesame seed oil. A peroxide titer value of 35.7 meq/kg. has been attained for the sesame seed oil-sulfur-oxygen treated composition while sesame seed oil oxidized alone at 137 DEG C. yields a value of 63.3 meq/kg. a peroxide titer value of 35.7 meq/kg [.DELTA.=(35.7-18.8)=16.91] has been attained for the sesame seed oil--sulfur--oxygen treated composition while sesame seed oil without sulfur oxidized at 137 DEG C. yields a value of 63.3 meq/kg [.DELTA.=(63.3-10.2)=53.1].

*J. Sci Fd. Agric. 1975, 26, 1353-1356.

Generally a substantial increase in the peroxide titer value can be defined as .DELTA.3 to about .DELTA.100 in cases where sulfur is incorporated into the composition and an from about .DELTA.3 to about .DELTA.400 when the oil is oxidized alone, or in the absence of sulfur.

The process used for determining the peroxide titer values discussed and reported herein are determined by placing a 2 gr. sample of the composition in a flask purged with nitrogen, and adding thereto 2 ml. of concentrated acetic acid and 0.5 grams of KI. The mixture is capped to exclude air and allowed to remain in the dark for 30 minutes to complete the reaction. The side walls are then wet down with a minimum of water and approximately 1-2 ml of a 2% starch added thereto. The solution is then immediately titrated to the end point with 0.007 normal Na2 S2 O2 solution. The end point is white when small amounts of peroxides are present and slightly when larger amounts are present.

The compositions as prepared according to the process of this invention should be used soon after preparation as there is indication that the peroxide titer values and effectiveness of the compositions decrease upon aging.

Preferred compositions according to this invention can be prepared by adding the sulfur to the oil, such as sesame oil, and heating the mixture with agitation at a temperature not to exceed about 130 DEG C. It is preferable or advantageous to heat the mixture between 120 DEG and 127 DEG C. Heating the mixture above about 130 DEG C. for a sufficient time causes a progressive color change in the mixture and otherwise appears to be detrimental. The temperatures given above relate to the use of sulfur with sesame oil. The ranges of temperatures which can be used to produce the compositions made according to this invention may vary with the particular oil being used, but generally a temperature of 120 DEG C., preferably 125 DEG C. to 127 DEG C., will be sufficient for most oils when sulfur is added.

If the oil and sulfur is heated below about 90 DEG C., it is difficult to incorporate the sulfur into the oil by heating and stirring means. The best results have been obtained to date by maintaining the temperature used in forming the compositions over a prolonged period of time from about 30 minutes to one hour. Stirring aids in the reaction, and experiments to date indicate that a fairly violent stirring is advantageous. The introduction of air into the mixture during the heating is also very advantageous, particularly when the mixture is not subjected to prolonged heating and is the preferred method. The stirring can be accomplished with the introduction of the air.

After the reaction has taken place, it is cooled. Sulfur crystals remaining in the bottom of the reaction vessel can easily be removed by filtration. The remaining fluid is ready for use after appropriate sterilization for injection or incorporated into capsules, such as gelatin, for oral administration.

The amount of sulfur incorporated into the oil is advantageously between about 0.1% to 2.5% by weight, based on the oil. If higher amounts of sulfur are used they generally precipitate out. There appears to be no advantage to using higher amounts of sulfur in any event since the ultimate dosage given to the patient is the criteria rather than the amount of sulfur content in the oil.

As can be observed from Example 2 below, the incorporation of the sulfur into the oil seems to be limited to about 1% by the process presently being used to produce the sulfurized unsaturated oils.

The sulfur content can be much less than about 1% if desired and smaller sulfur content is advantageous when administered by injection. Varying the amount of sulfur below about 1%

incorporated in the polyunsaturated oils for oral administration only affects the number of capsules to be taken at a given time by a particular patient.

Experiments to date indicate that the optimum sulfur content for oral administrations is about 1% and by injection about 0.1% to 0.3% by weight of the sulfur based on the weight of the oil.

The dosage prescribed to a patient will, of course, vary depending upon theparticular patient and the number of cigarettes being smoked a day. In general, a daily dose of 3-5 capsules containing 1 ml of the sulfurized oil for the first three days after which the dose is progressively reduced. For example, for a heavy smoker it is advantageous for the patient to take about 8 capsules containing 1 ml of the sulfurized oil containing about 1% sulfur for the first three days and take 3 or 4 capsules a day for the next four days. This is generally sufficient to eliminate or reduce the desire or need for tobacco. The desire or need for tobacco generally disappears from the patient within 2-3 days. This single treatment may last for months. However, the patient can be given an additional supply of the encapsulated sulfurized oil and directed to take additional capsules if he feeds any desire or need for tobacco.

When the sulfurized oil is used by injection, such as intramuscularly or intraperitoneally, it is advantageous to have the sulfur contained in the sulfurized oil below about 0.5% by weight, preferably between about 0.1% to 0.3% by weight, and to inject from 1/2 to 3 ml of this solution into the patient. Experiments to date indicate that the injection of sulfurized oil is somewhat painful when it contains above about 0.3% sulfur. Administration by injection is, of course, not necessary, but it may act faster initially. Generally if a person is given the injection of the sulfurized oil, he can also be given a supply of the oral capsules and directed to take 3 to 4 capsules a day following the injection for one week.

EXAMPLE 1

A sulfurized oil was prepared by mixing 50 grams of sublimed sulfur, obtained from Fisher Scientific, with one liter of sesame oil. The mixture was heated under fairly rapid agitation by air to a temperature of about 127 DEG C. until all of the sulfur was incorporated into the sesame oil. The reaction mixture was then cooled to room temperature, producing at the bottom of the reaction vessel a small amount of sulfur crystals. The crystals were then separated from the liquid by filtration and about half of the crystals replaced in the resulting liquid, wherein they slowly dissolved.

The resulting sulfurized oil was then incorporated into gelatin capsules in the amount of 1 ml per capsule.

Four patients reported that they had been smoking three to four packs of cigarettes a day. The patients were given 5 of the above capsules the first day and directed to take 5 capsules on the second and third days and 3 capsules for each of the four days remaining in the week. The patients reported no strong desire for tobacco after the third day and reduced their smoking habits to three to four cigarettes a day without nervousness or withdrawal symptoms.

Another patient who was smoking 60-80 cigarettes a day for the last 20 years was given 8 capsules of 1 ml of 1% sulfur in oil for three days. She remained without discomfort during this period. The treatment lasted 10 days with progressive reduced doses. The patient did not

smoke for four months without the need for desire for smoking tobacco.

A number of other persons who were chronic smokers of varying degrees were also given the same dosage. Over all, based on the total number of persons so treated about 80% had an almost immediate loss of the desire to smoke while about 50% of the remaining persons felt a considerable loss of the desire to smoke after some time had passed while continuing the treatment. The remaining persons apparently did not lose their desire to smoke.

EXAMPLE 2

4 g. of sulfur were weighed out and placed in an Erlenmeyer flask. 200 ml of sesame oil were added; the contents were heated to 125 DEG C. with stirring until the sulfur dissolved. The flask was removed from heat and allowed to cool to room temperature (5 hours). Sulfur crystals were filtered into a Buchner funnel, washed thoroughly with hexane to remove residual oil, and weighed.

The above example was repeated three times. The washed sulfur recipitated was weighed in each trial and the amount of sulfur in the sesame oil calculated by difference as follows:

Initial weight of sulfur: 4.00 g
Weight of sulfur ppt.:
Trial 1 2.05 g
Trial 2 2.00 g
Trial 3 1.92 g
% (w/v) sulfur in sesame oil:
Trial 1 1.02%
Trial 2 1.00%
Trial 3 0.99%
Average 0.99%

From this it was concluded that the solutions contained approximately 1% sulfur after filtration.

The invention also includes the use of selenium in place of elemental sulfur and for the same use. When using selenium it is combined with the allylic moiety in the same manner as sulfur but heated to a temperature in the range of 230 DEG to 250 DEG C., preferably about 240 DEG C. from 15 minutes to an hour or more or until the peroxide titer value is substantially greater than that of the untreated allylic moiety in the same manner as disclosed herein with respect to the use of sulfur. Those compositions into which selenium is incorporated have to date not indicated as good an effect as those composition into which sulfur is incorporated.

Method of employing therapeutic composition comprising ammonium or substituted ammonium compounds for treatment of alcoholism US4346082

This invention relates to a method of treating alcoholism and for eliminating, reducing or preventing alcohol intoxication or the manifestations of alcohol intoxication in humans by

administering thereto a therapeutic composition comprising an ammonium compound or compounds, said compounds and each of said compounds having a pH greater than 5.0 when in aqueous solution at a concentration of 5 grams per 100 grams of solution (5 weight percent), and particularly ammonium salt compounds containing ammonium cations and sulfur anions.

BACKGROUND OF THE INVENTION

Various pharmaceutical uses of ammonium compounds have long been recognized. For example, the following ammonium compounds (as listed in Hackh's Chemical Dictionary, 4th Ed. McGraw-Hill, New York pages 37-40) have the following medicinal uses as indicated therein. Ammonium acetate is used as an antipyretic and diaphoretic antidote in formaldehyde poisoning; ammonium benzoate has been used as an antipyretic, diuretic and alternative; ammonium bromide is used to treat neuralgia; ammonium carbamate is used as a stimulant; ammonium carbonate carbamate (Hartshorn salt) is used as a heart stimulant; ammonium chloride is used as an expectorant, stimulant diuretic or disphoretic, as well as externally; ammonium formate is used as an antiseptic; ammonium hypophosphite is a nerve tonic; ammonium thiosulfate can be used as an antiseptic, ammonium iodide is used to treat syphilis and leprosy; ammonium persulfate is used as a disinfectant; ammonium phosphate can be used as an antirheumatic; ammonium salicylate is used as an antirheumatic, antipyretic, expectorant, and bactericide; and ammonium valerate is a hypnotic, sedative, and tonic. Ammonium thiosulfate has long been a standard industrial commodity, and U.S. Pat. No. 3,350,168 to Ziegler indicates that U.S. consumption of ammonium thiosulfate totaled 30,000 tons per year at the time of such patent. U.S. Pat. No. 3,890,428 to Jayawant and U.S. Pat. No. 3,973,793 to Netzger et al. indicates that ammonium thiosulfate has long been employed as a photographic fixer.

A publication entitled "Testing for a `Sobering Pill`," DOT HS-801 208 (1974), available from National Technical Information Service, Springfield, Va. 22151, discloses that a number of compounds, including ammonium chloride, were investigated to determine their potential for blocking or neutralizing the effect of alcohol on a human brain. While the most effective amethystic agent (a preventive antidote of drunkenness) found was L-dopa, with respect to ammonium chloride, which has a relatively low molar pH in aqueous solution, the publication concludes that ammonium chloride does not appear to act as an amethystic agent.

None of the reference teaches the use of the compositions of the present invention as a treatment for alcoholism or eliminating and preventing alcohol intoxication or the manifestations of alcohol intoxication.

SUMMARY OF THE INVENTION

The invention relates to a method of treating alcoholism and for eliminating, reducing or preventing alcohol intoxication or the manifestations of alcohol intoxication in humans by administering thereto an ammonium compound or compounds, said compounds and each of said compounds having a pH greater than 5.0 moles when in aqueous solution at a concentration of 5 weight percent. Especially preferred embodiments are the salt compounds containing ammonium cations and sulfur anions. The ammonium compound can be administered to the patient by various known methods of injection or orally as by capsule form.

DETAILED DESCRIPTION OF THE INVENTION

It is to be especially noted that applicant is not claiming a cure for alcoholism; rather, this invention encompasses a method to treat acute and chronic effects of alcoholism or its manifestations or to prevent or reduce alcohol intoxication in which are used therapeutic compositions comprising any non-toxic compound having ammonium cations or substituted ammonium in its molecule, or mixtures or more than one such compound wherein said compound and each of said compounds have a pH greater than 5.0 when in aqueous solution at a concentration of 5 weight percent. Such preparations administered to humans may also help in detoxification of patients addicted to alcohol.

Concerning the aforesaid pH requirement, it is to be observed that, for example, within a series of ammonium salts of a polybasic acid the most preferred therapeutic agent is that molecule with no acidic hydrogen ion; the next most preferred is that molecule with one acidic hydrogen ion, and the least preferred is that with only one ammonium ion. For example, triammonium phosphate is preferred over diammonium monohydrogen phosphate, which in turn is preferred over monoammonium dihydrogen phosphate.

Also comprising a class of preferred embodiments are those agents containing sulfur in the anion portion of the molecule. Exemplary of effective agents containing sulfur are ammonium thiosulfate, ammonium sulfate, ammonium sulfamate and ammonium tetrathionate. The most effective of these is ammonium thiosulfate, with ammonium sulfate for treatment of the effects of alcohol in humans being somewhat less effective.

Ammonium acetate has likewise been shown to be a preferred embodiment of the instant invention.

Especially preferred are those ammonium salts of weaker acids and the most basic ammonium salts of polyprotic acids, that is, salts with comparatively basic aqueous solutions. To exemplify the preferred anions, namely those forming aqueous solutions with a pH greater than 5.0 at a concentration of 5 weight percent (5 grams of salt per 100 grams of solution), the following table gives measured pH values for certain salt species mentioned in this application.

TABLE I
pH of 5 Weight Salt Percent Solution
Ammonium thiosulfate
5.966
Ammonium sulfamate
5.335
Ammonium acetate 6.790
Ammonium sulfate 5.263
Ammonium chloride
4.761

For each salt, 5.000 grams of reagent grade material was weighed and added to 95.00 grams of water. An Orion Ionalyzer Model digital 801 pH meter with glass electrode measured against a saturated calomel electrode was standardized by a pH 7.00 buffer. The instrument was allowed to equilibrate for three minutes between each sample, and the electrodes were rinsed with carbonate-free deionized water. Manual temperature control was set at 25 DEG C.

After the last sample was measured, the instrument was checked by measuring the pH 7.00 buffer solution and the first sample, and consistent readings were obtained.

Also contemplated within the scope of this invention are cations containing substituted ammonium, where one or more of the four hydrogen atmos attached to the nitrogen is substituted with, for example, an alkyl group such as methyl or ethyl. Such compounds are well recognized in the art, and the same preferred anions outlined above are preferred when combined to form salts of substituted ammonium cations. Only those anions which form nontoxic compounds with substituted ammonium cations are contemplated as within the scope of this invention.

It is contemplated that the dosage of the compound or compounds encompassed within the scope of this invention would be limited to that dosage normally toxic to a human subject, as determined by both body weight and the particular physiological constitution of the human subject. Furthermore, it is contemplated to limit the dosage of the compound or compounds of the invention to that dosage which, when given with alcohol, constitutes a non-toxic amount.

Notwithstanding the requirement that compositions falling within the scope of the instant invention be nontoxic, studies of acute subacute and chronic toxicity of ammonium thiosulfate, ammonium sulfate and ammonium acetate in mice and rats have shown a low toxicity for their administration through gastric catheter. Studies in humans have demonstrated likewise the nontoxicity of ammonium thiosulfate, ammonium sulfate and ammonium acetate to the extent that even repeated administration of up to 20 capsules per day (1 gram/capsule) for a period of 10 days produced no clinical or analytic noxious effects.

The compositions of the present invention can be prepared and suitably administered in any of a number of conventional ways, such as by incorporating the compound or compounds into gelatin capsules or any other conventional soluble capsule, in an amount up to about 1.2 grams of the compound or compounds per capsule; preferably the capsules should contain either about 0.5 grams or about 1.0 gram. The compound or compounds may also be administered in any conventional tablet form which may contain the same amount of the compound or compounds as the capsule. Likewise, the composition may be consumed orally in a non-capsule or non-tablet form, i.e., in a solution comprised of the compound or compounds of the invention, and, for example, a pharmaceutically acceptable carrier, or diluent, such as sterile water, wherein the solution may contain up to about 70% by weight of the compound or compounds of the invention. It may thus be administered in dropwise form until the desired equivalent amount of the compound or compounds is administered.

The compound or compounds of the invention may also be administered by injection, such as intramuscularly or intraperitoneally, wherein the solution to be injected comprises the compound or compounds of the invention and any conventional inert pharmaceutically acceptable carrier, or diluent, such as sterile water, and wherein the solution may contain up to about 10% by weight of the compound or compounds of the invention. The amount to be injected will depend on the equivalent amount of the compound or compounds that one desires to administer.

Although, as noted, the agents of the present invention can be injected in aqueous solution into the body, it is preferred that they be administered orally encapsulated in a conventional soluble capsule containing in solid form the prescribed dosage of preparation.

Concerning the specific amounts of the compound or compounds to be administered, this will be easily determinable by those skilled in the art and will depend, to a certain extent, upon the particular compound or compounds to be administered (for instance, it has been found that twice as much of ammonium sulfate and ammonium acetate as compared to ammonium thiosulfate is required to achieve the same result), whether one is treating those already subject to the effects of alcohol and exhibiting the manifestations of alcohol, or whether one is treating individuals so as to prevent the manifestations of alcohol from occurring in the first instance. It has been found to be an advantageous mode of preventing intoxication to administer to a patient one capsule containing approximately 1 gram of ammonium thiosulfate (twice the dosage for ammonium sulfate or ammonium acetate) approximately 40 minutes before consumption of the first intoxicating alcoholic drink and a second capsule after the third drink. In this manner, it was shown that approximately 5 to 7 alcoholic drinks may be consumed without any outward evidence of inebriation.

Another preferred mode for the application of the instant invention in the treatment of persons already partially subject to the effects of alcohol and exhibiting the manifestations of alcohol intoxication (i.e., after one or two alcoholic drinks) is to administer either one or two capsules, each containing approximately 1 gram of ammonium thiosulfate (or approximately 2 to 4 capsules, each containing 1 gram of ammonium sulfate or ammonium acetate).

For the treatment of those habitually addicted to alcohol, it has been found preferable to administer about 4 to 6 grams/day, i.e., 4 to 6 capsules, each containing 1 gram of ammonium thiosulfate (or approximately twice the dosage as in the case of ammonium sulfate or ammonium acetate) for two days and thereafter to reduce the dosage to approximately 1 to 2 grams/day as required.

A possible explanation for the activity of the ammonium salts of this invention is that such compositions counteract the effects in the body of fatty acids, and prevents conjugation of substances with positive polar groups. Any suggested mode of operation or explanation of the mechanism of activity of the present invention is not intended to limit the scope of the present invention, and an understanding of such mode or mechanism is not necessary for the successful practice of the present invention.

Tests of some of the compounds encompassed within the scope of this invention were carried out with mice to determine efficacy in altering the effects of alcohol administered to the test animals. Good results on the mice were also obtained with the use of ammonium acetate. A series of tests comparing the effects on mice of ammonium thiosulfate and ammonium sulfate indicate that both are approximately equally effective. It is expected, however, that the effect of ammonium thiosulfate in altering the effects of alcohol ingestion in humans is substantially greater than the effects of ammonium sulfate. Tests of some of the compounds encompassed within the scope of this invention were carried out with humans, and likewise, good results were obtained which demonstrate the efficacy of the instant invention.

Throughout the specification and claims reference to an alcoholic drink means reference to an aqueous mixture of ethanol containing about 15-25 grams of ethanol per drink.

EXAMPLE 1

Procedure--The following procedure was carried out for determining the ED50 (effective dose which produces the desired effect in 50% of the test animals) of 30% (v/v) ethanol for

neurological deficiency in fasted mice which had been previously pretreated with an aqueous solution of ammonium thiosulfate: Food, but not water, was removed from the cages of 50 adult male albino mice (Charles River) on the day of the test. Five hours later the fasted animals were pretreated orally with 0.6 ml/mouse of a 10% aqueous solution of ammonium thiosulfate. Thirty minutes later a freshly prepared solution of 30% (v/v) ethanol was administered orally to the animals in groups of 10, at doses ranging from 0.5 to 1.0 ml per mouse. Ten minutes after administering the ethanol the mice were placed individually on a rod rotating at 6 rpm. Neurological deficit was recorded if the animal was unable to remain on the rod for at least 10 seconds. A group of 10 fasted but non-pretreated mice all exhibited neurological deficit following a dose of 0.5 ml, thereby serving as controls on the activity of the freshly prepared ethanol solution.

Findings for individual animals (+)=neurological deficit, and (-)=no neurological deficit are shown below in Table II with the summary of results set forth in Table III. The oral ED50 of ethanol in the ammonium thiosulfate solution pretreated animals is shown to be 0.76 ml, with 95% fiducial limits of 0.65 to 0.90 ml (determined graphically by a Litchfield and Wilcoxon plot).

The identical procedure was carried out for determining the oral ED50 of 30% (v/v) ethanol for neurological deficit for non-pretreated mice: Freshly prepared 30% (v/v) ethanol was administered orally to adult male albino mice (fasted for 5 hours), in groups of 5 to 10, at doses ranging from 0.05 to 0.50 ml per mouse. Ten minutes later the animals were placed, individually, on a rotored, rotating at 6 rpm. Neurological deficit was again recorded (+) if the animal fell from the rod--i.e., did not possess the motor coordination required to `logroll`--in less than 10 seconds. Absence of neurological deficit was similarly recorded (+) if the animal had sufficient coordination and muscular power to remain on the rotating rod for 10 seconds or more. The results are depicted in Table IV and summarized in Table V wherefrom it is seen that the dose of ethanol required to induce neurological deficit in 50% of the untreated animals (i.e., in this test the mice were in no way pretreated by the composition of the instant invention) is 0.17 ml/mouse, and the 95% fiducial limits (Litchfield and Wilcoxon graphic method used) was 0.13 to 0.22 ml/mouse.

Further, and in order to avoid physio-chemical problems that might, albeit remotely, arise if ethanol is administered orally, applicant also determined the intraperitoneal ED50 of ethanol in fasted mice. The procedural details are identical to those followed in the case of the oral ED50 except that the ethanol (30% v/v) was injected intraperitoneally. These results reveal that the intraperitoneal ED50 of 30% ethanol is 0.15 ml/mouse (0.12-0.19 at 95% confidence limit) which is effectively the same as that obtained when ethanol was given orally. This latter finding confirms what has long been known, that ethanol is rapidly and fairly completely absorbed in the fasting state.

By so determining the ED50 in non-pretreated mice, one could obtain statistically meaningful relative results in respect to the efficacy for the pretreatment of mice with ammonium thiosulfate.

Results--The ED50 of 30% ethanol in non-pretreated mice was 0.17 ml/mouse; the comparable value for pretreated mice shown in the tables below is 0.76 ml/mouse. This establishes that following pretreatment with ammonium thiosulfate nearly five times as much ethanol was required to induce neurological deficit.

TABLE II
Results

Mouse No.	Weight (gm)	Ethanol (ml)	Thiosulfate Solution (ml)	Dose of (+) = Dose of (-) = Ammonium Fall 10 sec. No fall in 10 sec.
1	33	0.5	0	- Control+
2	33	"	"	+
3	30	"	"	+
4	34	"	"	+
5	33	"	"	+
6	32	"	"	+
7	33	"	"	+
8	35	"	"	+
9	36	"	"	+
10	39	"	"	+
11	26	"	0.6	-
12	24	"	"	-
13	22	"	"	-
14	26	"	"	-
15	29	"	"	-
16	25	"	"	-
17	25	"	"	-
18	25	"	"	-
19	25	"	"	+
20	30	"	"	-
21	23	0.75	0.6	+
22	26	"	"	DEG
23	29	"	"	-
24	26	"	"	-
25	24	"	"	+
26	26	"	"	-
27	24	"	"	+
28	29	"	"	-
29	30	"	"	-
30	28	"	"	-
31	31	1.00	0.0	+
32	29	"	"	+
33	27	"	"	+
34	30	"	"	+
35	26	"	"	+
36	30	"	"	+
37	28	"	"	+
38	29	"	"	+
39	23	"	"	+
40	29	"	"	+
41	26	0.63	0.6	-
42	28	"	"	+

43 29 " " -
44 26 " " -
45 29 " " -
45 29 " " -
46 28 " " -
47 27 " " -
48 27 " " +
49 29 " " -
50 29 " " -
51 27 0.87 0.6 +
52 23 " " +
53 27 " " -
54 25 " " +
55 26 " " +
56 24 " " +
57 27 " " -
58 25 " " +
59 27 " " -
60 27 " " +

TABLE III
Summary
Ethanol Fraction Falling
Percent ED50 (ml)
(ml Per Mouse)
From Rod in 10 sec.
Falling (95% Limit)
0.50 1/10 10
0.63 2/10 20
0.75 4/10 40
0.87 7/10 70 0.76
(0.65-0.90)
1.00 10/10 100

TABLE IV
Dose of Results
Mouse Weight Ethanol (+) = Fall 10 sec.
No. (gm) (ml) (-) = No fall in 10 sec.
1 22 0.5 +
2 22 " +
3 23 " +
4 22 " +
5 22 " +
6 22 0.1 -
7 24 " -
8 21 " -
9 22 " -
10 22 " -
11 22 0.5 +
12 22 -- +

13 24 " +
14 23 " +
15 18 " +
16 22 0.2 +
17 21 " +
18 23 " -
19 23 " -
20 21 " +
21 21 " +
22 24 " -
23 24 " +
24 22 " +
25 22 " +
26 20 0.1 -
27 23 " -
28 25 " -
29 22 " +
30 21 " +
31 21 0.15 -
32 21 " -
33 20 0.15 -
34 21 " -
35 22 " -
36 24 " +
37 20 " +
38 22 " +
39 22 " +
40 19 " +
41 20 0.05 -
42 20 " -
43 19 " -
44 23 " -
45 24 " -
46 19 0.30 -
47 21 " +
48 22 " +
49 21 " +
50 21 " +

TABLE V
Summary

Ethanol Dose Fraction Falling Percent ED50 (ml) (ml Per Mouse) From Rod in 10 sec. Falling (95% Limit)
0.05 0/5 0
0.10 2/10 20
0.15 4/10 40

0.20 7/10 70 0.17
(0.13-0.22)
0.30 4/5 80
0.50 10/10 100

EXAMPLE 2

This Example compares the effectiveness of ammonium thiosulfate and ammonium sulfate as inhibitors of ethanol-induced neurological deficit in fasted mice. Each composition was prepared freshly as a 10% aqueous solution from the crystalline preparation. A dose of 0.6 ml/mouse was administered orally to 10 mice for each compound. Thirty minutes later 0.5 ml/mouse of 30% (v/v) ethanol was given orally to each mouse and, 10 minutes later, the animals were tested for the presence or absence of neurological deficit in the usual manner as described in Example 1. A group of 10 untreated mice were used as controls. The results are shown in Table VI with the summary of the results in Table VII.

Results--It is clear that both ammonium thiosulfate and ammonium sulfate were highly effective as inhibitors of ethanol-induced neurological deficit at the dose used. It is equally clear that the two compounds were essentially equipotent on the basis of this single test.

TABLE VI
Results
(+= Dose of Fall in 10 sec.
Mouse Weight 30% Ethanol (-) =
No. (gm) (ml) No Fall in 10 sec.
Dose of Ammonium Thiosulfate (ml)
1 29 0.6 0.5 -
2 29 " " -
3 28 " " -
4 27 " " +
5 28 " " -
6 25 " " "
7 27 " " -
8 26 " " -
9 26 -
10 26 " " +
Dose of Ammonium -- sulfate (ml)
11 27 0.6 " -
12 28 " " +
13 29 " " +
14 27 " " -
15 30 " " -
16 25 " " -
17 30 " " +
18 28 " " -
19 30 " " -
20 26 " " -
21 30 Control - no " + pretreatment
22 28 " " +
23 24 " " +

24 25 " " +
25 26 " " +
26 27 " " +
27 25 " " +
28 25 " " +
29 28 " " +
30 26 " " +

TABLE VII
Summary
Dose
ml/mouse No. Protected/
Compound
Ethanol Route No. Treated
Ammonium thiosulfate
0.6 0.5 Oral 8/10
+ 30% Ethanol
Ammonium sulfate + 0.6 0.5 Oral 7/10
30% Ethanol
0 0.5 Oral 0/10

EXAMPLE 3

This Example sets forth the oral Ed50 of ammonium thiosulfate vs. ethanol-induced neurological deficit in fasted mice. The mice used in this study appeared to be in good health. They were deprived of food, but not water, for a period of five hours preceding the test. A 10% aqueous solution of ammonium thiosulfate was prepared from the crystalline material and appropriate amounts of distilled water were added to provide solutions containing 7.5, 5.0, 2.5, and 1.25% ammonium thiosulfate. A dose of 0.6 ml/mouse of all five ammonium thiosulfate solutions was administered orally. Ten minutes later the animals were tested for neurological deficit or its absence in the usual manner as described in Example 1. A separate group of fasted by non-pretreated mice served as ethanol controls. The results are set forth in Table VIII and summarized in Table IX.

Results--It is shown that, using 0.6 ml/mouse as the basic dose, the percent of pure ammonium thiosulfate required to protect 50% of the mice against ethanol-induced neurological deficit was 3.6 (2.63-4.93%).

TABLE VIII
Results
Percent (+) =
Ammonium Dose Fall in 10 sec.
Mouse Weight Thiosulfate 30% Ethanol
(-) =
No. (nm) (0.6 ml/mouse)
(ml/mouse)
No Fall in 10 sec.
1 32 10.0 0.5 +
2 32 " " -
3 27 " " -

4 29 " " -
5 31 " " -
6 34 " " -
7 34 " " +
8 32 " " -
9 35 " " -
10 35 " " -
11 34 7.5 " -
12 28 " " -
13 35 " " -
14 32 " " -
15 31 " " -
16 33 41 " +
17 33 " " -
18 30 " " -
19 35 " " +
20 32 " " -
21 30 5.0 " +
22 31 " " +
23 30 " " -
24 28 " " -
25 33 " " -
26 32 " " -
27 34 " " +
28 32 " " -
29 31 " " -
30 30 " " -
31 31 2.5 " +
32 30 " " -
33 " " +
34 31 " " +
35 34 " " +
36 34 " " +
37 28 " " -
38 29 " " +
38 29 " " +
39 30 " " +
40 30 " " +
41 30 1.25 " +
42 34 " " +
43 29 " " +
44 33 " " +
45 36 " " +
46 33 " " +
47 32 " " +
48 31 " " +
49 30 " " +
50 32 " " +
51 32 0 - Control " +
52 33 " " +

53 33 " " +
54 33 " " +
55 36 " " +
56 35 " " +
57 30 " " +
58 32 " " +
59 33 " " +
60 31 " " +

TABLE IX
Summary
Dose of Dose of Ammonium Ammonium 95%
Thiosulfate
Thiosulfate
Fraction Per- ED50
Confidence
(%) (ml/mouse)
Protected
cent (%) Limits

0 - Controls
-- 0.10 0
1.25 0.6 0/10 0
2.5 " 3/10 30
3.6 2.63-4.93
5.0 " 7/10 70
7.5 " 8/10 80
10.0 " 8/10 80

EXAMPLE 4

More than one hundred individuals who had consumed 1 or 2 alcoholic drinks, and who had thus demonstrated certain and typical early manifestations of the effects of the alcohol, were given 1 or 2 capsules, each containing 1 gram of ammonium thiosulfate. These individuals were thereafter able to consume additional alcoholic drinks, in some cases, up to 8 additional drinks without exhibiting any of the typical and usual manifestations of the effects of alcohol.

Method for treating alcoholism and eliminating and preventing alcohol intoxication
US4368206

The invention relates to a method of treating alcoholism and for aiding in controlling alcohol intoxication in humans by the internal administration of a composition produced by heating certain allylically unsaturated compounds sufficient to substantially increase the peroxide titer. The incorporation of sulfur in the composition during the heating has been found to be particularly advantageous.

BACKGROUND OF THE INVENTION

There has been much recent interest in the study of alcoholism involving biological, psychological, and sociological investigations. Publications such as the various "Proceedings of the . . . Annual Alcoholism Conference" and "Recent Advances in Studies of Alcoholism", obtainable from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, indicate the rather intensive scientific investigations in this area. Some of these studies are concerned with the effect on a host produced by certain chemicals in combination with alcohol.

An article by E. B. Truitt and M. J. Walsh appearing at p. 100 et sequa of "Proceedings of the First Annual Alcoholism Conference of the National Institute on Alcohol Abuse and Alcoholism", DHEW Publication No. (NIH) 74-675 (1973) discloses a number of chemicals and drugs which have been reported to have anti-alcohol effects. Included in this list are disulfiram (tetraethylthiuram disulfide--see also U.S. Pat. No. 2,567,814 Jacobsen et al), calcium carbimide (see also U.S. Pat. No. 2,998,350 de Grunigen et al), and thiocyanates which are used specifically for their anti-alcohol properties.

U.S. Pat. No. 3,860,719 Marshall discloses the use of 2-[(3,4-dichlorophenoxy)methyl]-2-imidazoline hydrochloride (fenmetozole HCl) for combating ethanol intoxication in mammals.

However, an article by H. B. McNamee et al "Fenmetozole in Acute Alcohol Intoxication in Man", Clinical Pharmacology and Therapeutics Vol. 17, Number 6, pp. 735-737 concludes that, within the scope of the subject study, fenmetozole does not antagonize or significantly modify acute effects of alcohol intoxication in humans.

Another publication entitled "Testing For a `Sobering Pill`" DOT HS-801 288 (1974) available from National Technical Information Service, Springfield, Va. 22151 discloses that nikethamide, propranolol, L-dopa, pipradrol, aminophylline, ephedrine, sted-eze, and ammonium chloride were investigated to determine their potential for blocking or neutralizing the effect of alcohol on a human brain; the most effective amethystic agent found was L-dopa.

J. L. Mottin, in an article entitled "Drug-Induced Attenuation of Alcohol Consumption" Quart. J. Stud. Alc. 34: 444-472 (1973) discussed, inter alia, the use of the following compounds re the subject title: disulfiram, citrated calcium cyanamide, and metronidazole.

Russian Inventor's Certificate 187250 discloses the use of the "thiolic" preparations--"unitol" and "dicaptol"--for use in treating alcoholism. The Merck Index (Eighth Edition) discloses that Dicaptol (BAL or British Anti-Lewisite) is 2,3-dimercaptopropanol and is marketed as a 10% solution in peanut oil with 20% benzyl benzoate. It is further asserted that in the U.S.S.R. a water soluble form is available under the name Unithiol or Unitiol and is 2,3-dimercapto-1-propanol sodium sulfonate.

U.S. Pat. No. 2,799,619 Seifter et al. discloses compositions comprising certain phenothiazines as effective for treatment of alcoholics while British Pat. No. 1,399,992 (Revici) discloses that compositions comprising certain organic ethers are useful for the treatment of alcoholism.

SUMMARY OF THE INVENTION

The invention relates to a method for treating the manifestations of alcoholism or alcohol intoxication by aiding in the control of the craving for alcohol, or by aiding in the control of alcohol withdrawal symptoms, or by aiding in the control of alcohol intoxication in a human, which comprises internally administering to a human in need thereof an oxidized composition produced by the process comprising oxidizing, at a temperature of between about 110 DEG C. and about 150 DEG C., a liquid composition containing at least one fatty acid or fatty ester having allylic unsaturation of the type
--CH.dbd.CH--CH2 --CH.dbd.CH--

and/or
--CH.dbd.CH--CH.dbd.CH--CH2 --

for a period of time sufficient to produce a peroxide titer substantially greater than that of the untreated compound, in a non-toxic amount sufficient to aid in the control of the craving for alcohol, or to aid in the control of alcohol withdrawal symptoms, or to aid in the control of alcohol intoxication in said person. The incorporation of sulfur into the composition during or before the heating of the compositions has been found to be particularly advantageous and represents the most effective composition found to date. The compositions can be administered to the patient by the various accepted methods of injection or orally in tablet or capsule form.

DETAILED DESCRIPTION OF THE INVENTION

It is desirable to have a method for treating or aiding in the treatment of alcoholism in a human by controlling the craving for alcohol, by controlling withdrawal symptoms, or by aiding in the control of alcohol intoxication in humans. It is further desirable to have a method for aiding the control of alcohol intoxication of a non-alcoholic person by reducing or eliminating the alcohol intoxication either before or after the intake of alcohol.

This invention relates to such methods of treatment involving the internal administration to a human host of a composition produced by oxidizing a liquid composition containing a fatty acid or fatty ester, structurally characterized by allylic unsaturation, for example, by bubbling air through the reaction mixture. The fatty acid or ester advantageously includes elemental sulfur and/or a conventional free radical initiator such as tertiary-butyl peroxide during the heating step.

The allylically unsaturated compound is preferably a naturally occurring oil, containing polyunsaturated fatty esters such as an animal, vegetable, or fish oil, especially a polyunsaturated vegetable oil. Sesame oil is a vegetable oil consisting largely of triglycerides and is the most advantageous composition found to date in the practice of this invention.

The composition utilized preferably should contain a significant percentage of molecular species having allylic moieties to render the compositions useful according to the invention indicated by the following partial structures
--CH.dbd.CH--CH2 --CH.dbd.CH--

and/or
--CH.dbd.CH--CH.dbd.CH--CH2

As indicated, the unsaturation can be conjugated or nonconjugated but the composition must contain allylic methylene hydrogen.

Such compositions, as the case may be, should be oxidized or heated in the presence of oxygen at a temperature in the range between about 110 DEG C. and about 150 DEG C. The oxygen can be obtained by merely heating the composition open to the atmosphere but preferably and advantageously, the source of oxygen is a gas such as air injected into a heated oil such as sesame oil. The injected air also serves as a source of agitation.

As previously stated it is most advantageous to add elemental sulfur such as sublimed, precipitated, or washed sulfur to the compositions so that the sulfur is present with oxygen during at least a portion of the heating period and the sulfur incorporated into the composition. Additionally, a previous batch of the oxidized oil with or without sulfur or any commonly known and available free radical initiator, such as tert-butyl peroxide, may advantageously be present during at least a portion of the heating period.

If sulfur is added to the selected composition, for example, sesame oil, the temperature should be maintained at an upper limit within the range of about 120 DEG C. to about 130 DEG C., and preferably 125 DEG C. and 127 DEG C. These temperature limitations are based on a heating time of about one-half hour. The temperatures can be altered within limits depending on the time of heating. For example, the temperature can be 129 DEG-130 DEG C. if the time is shorter or even at 140 DEG C. for very short period of time. High temperatures for a prolonged period of time tend to degrade the composition and should thus be avoided.

If sulfur is not present during the heating period, the temperature should be maintained in the range between about 110 DEG C. and about 150 DEG C., and preferably in the range between about 120 DEG C. and about 140 DEG C.

The heat treatment is conducted for a period of from about 15 minutes to about two hours. If sulfur is present, optimal results are obtained if the heat treatment is conducted for a period of time between about 30 minutes to about 1 hour. If a free radical initiator is present, or if a selected composition inherently contains a significant amount of initiator, the heat treatment period may be conducted for a relatively shorter period of time.

The precise nature of the composition which results from the above-described treatment or the identity of the effective component or components is not presently known to the Applicant. However, while Applicant does not wish his invention limited by the following theory or fact, or mixed theory and fact as the case may be, certain evidence is available which indicates that an efficacious composition for the treatment of alcoholism or the control of intoxication in a human can be produced according to this invention.

In particular, it appears that a correlation exists between a composition useful for the subject purpose and its presumed peroxide or hydroperoxide content. By adhering to the process according to this invention, it has been found that efficacious compositions are produced which yield a significant peroxide titer when monitored by conventional iodometric analysis, the results being expressed, for example, in terms of microequivalents per gram or milliequivalents per kilogram. By significant peroxide titer is meant a value obtained which is greater than that which inherently may be present in the initial untreated compound.

In the case of triglycerides which contain the allylic type unsaturation as described above, the resulting oxidized species is thought to be a hydroperoxide represented by the following partial structure ##STR1## as interpreted via UV spectroscopic analysis, inter alia.

The data of Examples 3 and 4 below are consistent with the foregoing hypothesis. Trilinolein, the triglyceride of linoleic acid (9,12-octadecadienoic acid), the principal diunsaturated fatty ester in sesame oil, is subjected to the preferred treatment with air and sulfur. The resultant product has a number of properties characteristic of comparably treated sesame oil. Furthermore, its action mimics that of the treated sesame oil product in a primate model. Trilinolein is typical of a polyunsaturated oil, as is sesame oil, which contains about 35-47% linoleic acid residues in the total triglycerides.

Whatever the nature of the oxidized species, it appears amenable to monitoring by conventional iodometric analysis with or without the addition of sulfur.

Although it appears that the activity of the composition is coincident with the presence of peroxides or hydroperoxides, the efficacious agent need not necessarily be directly derived from these classes. It may in fact be those species derived from radicals resulting from decomposition of compounds of this class and may involve reaction with other molecules of, for example, triglyceride oils or sulfur including olefinic polymerization products and/or lower molecular weight decomposition products of the oils or additional products with sulfur such as sulfides, disulfides, hydropersulfides, etc.

With regard to a preferred embodiment, it appears that the presence of elemental sulfur (approximately 1% by weight based on sesame seed oil) during the oxidation of sesame seed oil acts to increase the amounts of oxidation products (conjugated hydroperoxides, diene, triene, unsaturated carbonyl) and that this increase appears optimal near 127 DEG C. as evidenced by UV spectroscopic analysis studies. In the absence of sulfur, it appears that the region near 137 DEG C. is optimal for the production of oxidation products.

As mentioned above, it appears that the most effective compositions are those which have a relatively high peroxide titer. Comparisons of preferred compositions, namely sesame seed oil or other polyunsaturated oils treated with air in the presence of sulfur, with other triglycerides, or triglyceride containing oils, including corn oil, cottonseed oil, and triolein with regard to their respective peroxide titers indicates a trend in peroxide levels concordant with observed bioactivity in alcoholics. Such trend of bioactivity agrees in general with the results of a peroxide analysis involving the above-identified oils in their untreated state and when oxidized in the presence of elemental sulfur under similar conditions as follows:

PEROXIDE ANALYSIS (meq./kg.)
"B"
Oil Used "A" Oil Treated*
.increment. = "B - A"
(Peroxide Oil Saturated With Sulfur Difference In Analysis)
With Sulfur and Air Peroxide
Sesame Seed
18.8 35.7 16.9
(10.2)
Corn 11.3 14.9 3.6
(6.8)

Cottonseed
10.9 10.2 -0.7**
(7.3)
Olive 12.4 13.8 1.4
(5.9)
Triolein 8.6 8.5 -0.1**
(7.2)
*Heated at 127 DEG C. for 0.50 hrs. with 90 l/min. air addition andrapid mechanical stirring and containing 1.0% elemental sulfur by weight.
**Within experimental error.

It is thought that a lower bioactivity and a lower peroxide titer of cottonseed oil is due to the presence of natural anti-oxidants. The elimination of the anti-oxidants from oils such as corn and cottonseed oil or the use of the relatively pure allylically unsaturated compounds or mixtures thereof will result in a substantially increased peroxide titer when treated according to this invention. Triolein contains only oleic acid moieties which are characterized by the allylically unsaturated group --CH.dbd.CH--CH2 -- and hence is quite difficult to oxidize,* particularly when compared to the preferred sesame seed oil or other polyunsaturated oils. A peroxide titer value of 35.7 meq/kg. has been attained for the sesame seed oil-sulfur-oxygen treated composition while sesame seed oil oxidized alone at 137 DEG C. yields a value of 63.3 meq/kg. A peroxide titer value of 35.7 meq/kg [.DELTA.=(35.7-18.8)=16.9] has been attained for the sesame seed oil-sulfur-oxygen treated composition while sesame seed oil without sulfur oxidized at 137 DEG C. yields a value of 63.3 meq/kg [.DELTA.=(63.3-10.2)=53.1].

*J.Sci. Fd Agric. 1975, 26, 1353-1356.

Generally a substantial increase in the peroxide titer value can be defined as .DELTA.3 to about .DELTA.100 in cases where sulfur is incorporated into the composition and as from about .DELTA.3 to about .DELTA.400 when the oil is oxidized alone, or in the absence of sulfur.

The process used for determining the peroxide titer values discussed and reported herein are determined by placing a 2 gr. sample of the composition in a flask purged with nitrogen, and adding thereto 2 ml. of concentrated acetic acid and 0.5 grams of KI. The mixture is capped to exclude air and allowed to remain in the dark for 30 minutes to complete the reaction. The side walls are then wet down with a minimum of water and approximately 1-2 ml of a 2% starch added thereto. The solution is then immediately titrated to the end point with 0.007 normal Na2 S2 O3 solution. The end point is white when small amounts of peroxides are present and slightly yellow when larger amounts are present.

The compositions as prepared according to the process of this invention should be used soon after preparation as there is indication that the peroxide titer values and effectiveness of the compositions decrease upon aging.

Preferred compositions according to this invention can be prepared by adding the sulfur to the oil, such as sesame oil, and heating the mixture with agitation at a temperature not to exceed about 130 DEG C. It is preferable or advantageous to heat the mixture between 120 DEG and 127 DEG C. Heating the mixture above about 130 DEG C. for a sufficient time causes a progressive color change in the mixture and otherwise appears to be detrimental. The

temperatures given above relate to the use of sulfur with sesame oil. The ranges of temperatures which can be used to produce the compositions made according to this invention may vary with the particular oil being used, but generally a temperature of 120 DEG C., preferably 125 DEG C. to 127 DEG C., will be sufficient for most oils when sulfur is added.

If the oil and sulfur is heated below about 90 DEG C., it is difficult to incorporate the sulfur into the oil by heating and stirring alone. The best results have been obtained to date by maintaining the temperature used in forming the compositions over a prolonged period of time from about 30 minutes to one hour. Stirring aids in the reaction, and experiments to date indicate that a fairly violent stirring is advantageous. The introduction of air into the mixture during the heating is also very advantageous, particularly when the mixture is not subjected to prolonged heating and is the preferred method. The stirring can be accomplished with the introduction of the air.

After the reaction has taken place, it is cooled. Sulfur crystals remaining in the bottom of the reaction vessel can easily be removed by filtration. The remaining fluid is ready for use after appropriate sterilization for injection or incorporated into capsules, such as gelatin, for oral administration.

The amount of sulfur incorporated into the oil is advantageously between about 0.1% to 2.5% by weight, based on the oil. If higher amounts of sulfur are used they generally precipitate out. There appears to be no advantage to using higher amounts of sulfur in any event since the ultimate dosage given to the patient is the criterion rather than the amount of sulfur content in the oil.

As can be observed from Example 2 below, the incorporation of the sulfur into the oil seems to be limited to about 1% by the process presently being used to produce the sulfurized unsaturated oils.

The sulfur content can be much less than about 1% if desired and smaller sulfur content is advantageous when administered by injection. Varying the amount of sulfur below about 1% incorporated in the polyunsaturated oils for oral administration only affects the number of capsules to be taken at a given time by a particular patient.

Experiments to date indicate that the optimum sulfur content for oral administrations is about 1% and by injection about 0.1% to 0.3% by weight of the sulfur based on the weight of the oil.

The dosage prescribed to a patient will, of course, vary depending upon the particular patient and the purpose for which he is being treated. For an alcoholic, for example, it is advantageous for the patient to take 5 capsules containing 1 ml of the sulfurized oil containing about 1 to 2% sulfur for the first 3 days and to take 3 to 4 capsules a day for the next 4 days. It is preferred that the patient be relatively sober when initiating the treatment. This is generally sufficient to eliminate or reduce the desire or need for alcohol. The desire or need for alcohol generally disappears from the patient within 24 hours. This single treatment may last for months. However, the patient can be given an additional supply of the encapsulated sulfur containing oil and directed to take a capsule if he feels any desire or need for alcohol.

When the sulfurized oil is used by injection, such as intramuscularly or intraperitoneally, it is advantageous to have the sulfur contained in the sulfurized oil below about 0.5% by weight, preferably between about 0.1% to 0.3% by weight, and to inject from 1/2 to 3 ml of this solution into the patient. Experiments to date indicate that the injection of sulfurized oil is somewhat painful when it contains above about 0.5% sulfur. Administration by injection is, of course, not necessary but it may act faster initially. Generally if a person is given the injection of the sulfurized oil, he can also be given a supply of the oral capsules and directed to take 3 to 4 capsules a day following the injection for one week.

To reduce alcohol intoxication, the patient is directed to take 2 to 5 capsules (containing 1 ml oil at 1% sulfur). The alcohol intoxication should generally disappear within about one hour.

To prevent alcohol intoxication 1 or 2 capsules (containing 1 ml oil at 1% sulfur) can be taken prior to beginning consumption of the alcohol or with the first drink.

EXAMPLE 1

A sulfurized oil was prepared by mixing 50 grams of sublimed sulfur, obtained from Fisher Scientific, with one liter of sesame oil. The mixture was heated under fairly rapid agitation by air to a temperature of about 127 DEG C. until all of the sulfur was incorporated into the sesame oil. The reaction mixture was then cooled to room temperature, producing at the bottom of the reaction vessel a small amount of sulfur crystals. The crystals were then separated from the liquid by filtration and about half of the crystals replaced in the resulting liquid, wherein they slowly dissolved.

The resulting sulfurized oil was then incorporated into geletin capsules in the amount of 1 ml per capsule.

A 50-year old patient, B. G., reported that he had been an alcoholic for 20 years consuming up to 1/5 to 1/2 gallon of hard liquor a day. The patient reported that he had tried hospitalization and different treatments without success. The patient was given 5 of the above capsules the first day and directed to take 5 capsules on the second and third days and 3 capsules for each of the 4 days remaining in the week. The patient reported no desire for alcohol after the first day and felt no need or desire for alcohol thereafter. The patient reported that he was feeling exceptionally fine.

Approximately 100 human patients have been treated to date according to this invention, including alcoholics, the social drinker when inebriated as well as to patients prior to the intake of alcohol. Significant results in controlling the craving for alcohol or controlling withdrawal symptoms or aiding in the control of intoxication were observed in approximately 80 percent of the patients treated.

EXAMPLE 2

4 g. of sulfur were weighed out and placed in an Erlenmeyer flask. 200 ml of sesame oil were added; the contents were heated to 125 DEG C. with stirring until the sulfur dissolved. The flask was removed from heat and allowed to cool to room temperature (5 hours). Sulfur crystals were filtered into a Buchner funnel, washed thoroughly with hexane to remove residual oil, and weighed.

The above example was repeated three times. The washed sulfur precipitate was weighed in each trial and the amount of sulfur in the sesame oil calculated by difference as follows:
Initial weight of sulfur: 4.00 g
Weight of sulfur ppt.:
Trial 1 2.05 g
Trial 2 2.00 g
Trial 3 1.92 g
% (w/v) sulfur in sesame oil:
Trial 1 1.02%
Trial 2 1.00%
Trial 3 0.96%
Average 0.99%

From this it was concluded that the solutions contained approximately 1% sulfur after filtration.

EXAMPLE 3

The preparation of Example 1 was repeated, except that trilinolein was substituted for sesame oil. The resultant product was significantly darker than the product of Example 1. A comparison of various properties of the oxidized, sulfurized trilinolein (OSTL) of this example with the oxidized, sulfurized sesame oil (OSSO) of Example 1 is shown in Table 1.

TABLE 1
Property OSTL OSSO
Peroxide No. (.mu.eq/g)
60.9 55
Dissolved Sulfur (%)
1.2 0.75
pH 4.8 6.7
Refractive Index (20 nD)
1.4831 1.4709
UV Absorption Significantly
Higher than at 254 nm. higher than untreated
OSSO oil
FTIR Difference Doublet at Doublet at
Spectrum* 940-990 cm@-1
940-990 cm@-1
*Fourier Transform Infrared Difference Spectrum, permitting identification of absorption peaks in the product not present in the spectrum of the starting material.

EXAMPLE 4

The oxidized, sulfurized sesame oil (OSSO) of Example 1 and the oxidized, sulfurized trilinolein (OSTL) of Example 3 were each tested for their efficacy in alleviating alcohol withdrawal symptoms in an alcohol-addicted monkey, using untreated sesame oil as a placebo. In each case, a monkey was addicted to ethyl alcohol by infusion of 5 ml/hr for 28 days of a solution ranging between 15 and 30% ethyl alcohol in normal saline. The ethyl alcohol solution was administered via an indwelling silastic catheter implanted into the jugular vein. The presence of and severity of withdrawal was evaluated according to the

presence and severity of specific symptoms, which are known to be exhibited by rhesus monkeys upon removal of alcohol in a dependent animal. Evaluation was based on a scale of 0: symptom not present, 1: mild presence of symptom, 2: moderate presence of symptom, and 3: severe presence of symptom. The symptoms evaluated were: generalized tremors, muscle fasciculations, elicited hyperreflexia, spasticity, rigidity, spontaneous hyperreflexia, fright, salivation, mydriasis, retching-vomiting, convulsive poses, convulsions, aggression, nervousness, excitability, and evoked threat.

During the 5-day placebo withdrawal period, which immediately followed the 28-day addiction period, the monkey received 5 ml of sesame oil injected into orange slices. The withdrawal symptoms were evaluated daily during this period. At the conclusion of the placebo withdrawal period, the animal was re-addicted to the ethyl alcohol over a 14-day period as described above. This was immediately followed by a 5-day drug withdrawal period. During this period, the animal received a daily dose of 5 ml of either OSTL or OSSO injected into orange slices and the daily withdrawal symptoms were evaluated. The results are shown in Table 2, where the lower the score, the less severe the symptoms and the more efficacious the therapeutic effect compared to placebo administration.

TABLE 2
Monkey Alcohol Withdrawal Scores
Daily Withdrawal Score*
Total
Test Treatment 1 2 3 4 5 Score

1 Placebo 9 12 10 10 10 51
1 OSTL 8(89) 6(50)
4(40)
4(40)
4(40)
26(51)
(% Reduction**)
2 Placebo 8 10 10 10 10 48
2 OSSO 4(50) 4(40)
3(30)
3(30)
3(30)
17(35)
(% Reduction**)
*Using rating instrument described above.

It can be seen from the data of Examples 3 and 4 that both the properties and the behavior of oxidized, sulfurized trilinolein and of oxidized, sulfurized sesame oil are quite similar, and show a similar ability to alleviate the symptoms of alcohol withdrawal in a reliable primate model.

The invention also includes the use of selenium in place of elemental sulfur and for the same use. When using selenium it is combined with the allylic moiety in the same manner as sulfur but heated to a temperature in the range of 230 DEG to 250 DEG C., preferably about 240 DEG C. from 15 minutes to an hour or more until the peroxide titer value is substantially greater than that of the untreated allylic moiety in the same manner as disclosed herein with

respect to the use of sulfur. These compositions into which selenium is incorporated have to date not indicated as good an effect as those compositions into which sulfur is incorporated.

Bismuth containing pharmaceutical compositions
US4851398

The invention relates to a method for making a composition which comprises selecting at least one fatty acid or fatty ester compound having an allylic unsaturation of the type -CH=CH-CH2-CH=CH- or -CH=CH-CH=CH-CH2-, adding to said compound a salt of an element having a rhombohedral crystal structure, such as Bi, Hg, As, B, Sb or Sm, to form a mixture, heating said mixture above about 260 DEG C. for a sufficient period of time to incorporate at least about 0.1% by weight of the element into the compound, cooling the mixture, and recovering the incorporated compound as the remaining fluid of the mixture. The invention also relates to the reaction products thus produced along with methods of administering these compositions to a subject to treat abnormal conditions caused mainly by a catabolic imbalance.

TECHNICAL FIELD

The present disclosure relates to anabolic agents of new lipidic compositions which have incorporated therein Bi or a similar element having a rhombohedral crystal structure, a method for preparing these compositions, and a method of use thereof to treat various conditions in a subject due mainly to a catabolic abnormality or imbalance.

SUMMARY OF THE INVENTION

The invention comprises novel compositions of lipidic materials, such as fatty acids, esters, or oils which include a group of elements having a rhombohedral crystal structure, such as Hg, Bi, As, Sb, B and Sm, incorporated therein. These compositions are made by heating the lipidic material to a temperature of at least about 260 DEG C. for a sufficient time to incorporate a predetermined amount of the element into the oil. At least about 0.1% can be used, although amounts between about 0.5 and 10%, preferably about 5%, are preferred.

These compositions of the invention are anabolic or anti-catabolic agents and may be administered to a patient who has a catabolic imbalance as evidenced by symptoms of certain diseases or adverse effects, to correct such imbalance, to treat the symptoms of diseases or adverse effects caused by the imbalance, as well as to have an antiviral action.

DETAILED DESCRIPTION OF THE INVENTION

Inspite of the most intensive research efforts, practically little progress has been obtained in the treatment of most diseases, and especially in the treatment of AIDS--today the modern lethal plague. The following represents the basis for an approach important also for the results of its clinical applications.

My research has shown the capital importance of the recognition of different pathogenic occurrences with direct application for the therapeutic approach. I have thus shown the existence of a dualistic pathogenesis, anabolic--constructive or catabolic--destructive state

which governs the biology in all its aspects. The normal state results from a dynamic balance between alternating anabolic and catabolic processes, while the abnormal state corresponds to imbalances due to the abnormal processes.

My new concept that the anabolic or catabolic character represents the fundamental aspect of a disease has put the problems of the pathological conditions from their pathogenesis to therapy entirely on a new basis.

Symptoms and analyses are serving to recognize the imbalance present and consequently to guide the choice and necessary amounts of appropriate agents to be administered. Fever, diarrhea, vomiting, nausea, perspiration, pain with an alkaline pattern, and insomnia represent the main symptoms of the catabolic imbalance. In blood analyses, the catabolic imbalance is evidenced by a high red cell sedimentation rate, eosinopenia, and leukopenia with high serum potassium. In the urinary system, characteristic analyses show a high oxyreduction potential, high specific gravity, low surface tension, low pH, and a low chloride excretion. The opposite symptoms and analyses correspond to an anabolic imbalance.

The further study of the cyto-histological changes have shown the anabolic imbalance to correspond to cells with manifest youth character, while the catabolic to correspond to old cells with pyknosis and kariorhetic changes. The study of these analyses has shown that while the oxyreduction is indicating a basic imbalance as related to the subnuclear level, other analyses, mainly the pH and the surface tension, are corresponding to superior level, and are consequently subject to more rapid and less general changes. While the oxyreduction provides information of a general more fixed basic imbalance, the pH and the surface tension are subject to more rapid and less basic changes. These considerations have special importance for the guided therapy.

Parallel to the recognition of the anabolic and catabolic imbalance, I studied the factors inducing them, to find the special role of the lipids. The study of the lipids in general has led to a new definition of these agents, as polar-nonpolar substances with the nonpolar group predominant. According to this research, the lipids represent the principal constituents, while the water-soluble fractions represent the secondary ones. The fact that the polar groups have electrostatic forces results in the existence of positively and negatively charged lipids. The most important positive lipids are the sterols, while the negative are the fatty acids.

It was found that the anabolic imbalances are directly related to the intervention of the lipids with positive polar groups, respectively, the sterols, while the catabolic imbalances result from the intervention of abnormal fatty acids, respectively, trienic conjugated compounds.

All the lipids of the body have their polar groups bound except for the brain and the red cells, which have free lipids. I have found that the lipids of the abnormal lesions are free, not combined, a fact which explains their special activity in the pathological conditions. As a direct consequence of this occurrence, I found that a lipid introduced in the body acts more directly upon the lesions.

I applied the dualistic concept for the study of the agents used therapeutically to find them to have either an anabolic or a catabolic character. I used an entire series of very concordant tests to determine this character. The study of the second day wound crust pH has shown a change toward more alkaline values for the agents with a catabolic action and more acid values for those with anabolic properties. The study of the curve of the surface of a healing

wound has shown the presence of several peaks of the curve. An anabolic agent makes these peaks disappear, while a catabolic agent increases their value or numbers.

The study of the influence exerted by agents upon the oxygen intake by cancer cells or of yeast has shown a reduction of oxygen intake for the anabolic agents and an increase for the catabolic agents. The anabolic agents also induce a leukocytosis with eosinophilia, a lower sedimentation rate, a lower serum potassium, as well as marked urine analyses - such as higher surface tension, lower specific gravity and higher pH. The catabolic agents provide opposite changes, in these blood and urine analyses. In general, the alcohols and amines induce anabolic changes while the acids, aldehydes and ketones induce catabolic changes.

I have studied under this specific dualistic aspect many different elements, and have found several important characters. The members of the same series (i.e., those in vertical rows) of the periodic table have all been found to have the same anabolic or catabolic character. The members of the odd A series and of even B series are anabolic, while those of the A even and B odd series, catabolic.

The study of the periodic table has shown another important character. All the members of the same period, i.e., those in horizontal rows, are predilectly working at the same level of the organization, with the lowest periods at the more primary or basic level. The 6th period (starting with cesium) is thus acting predilectly to the lowest organizational level of the subnuclear entities. The elements of the 5th period (of rubidium) are acting predilectly upon the nuclear level, while those of the 4th period (of potassium) upon the cellular level. The elements of the 3rd period (of sodium) act upon the tissue and organ levels, while those of the second period (of lithium) upon the general systemic level.

It was this special systemization of the elements which has its main application in the study of their biological actions. Of special interest are the elements of the 6th period, which are acting predilectly at the subnuclear level.

I have also shown that different biological independent entities correspond to different levels of the organization. For example, the viruses are thus recognized as subnuclear entities, while the microbes as nuclear entities and not as cells as erroneously considered.

As a direct consequence, it was recognized that the elements of the 6th period would have special action upon the subnuclear level formations of the complex individual and at the same time on the viruses as being entities corresponding to this special level. It was under this aspect that these elements were further studied. Cs, Hb, W, Os, Pt, Hg, Tl and Bi are members of the subnuclear level and were found to be anabolic agents having anticatabolic properties.

I have applied other findings to this study of the elements. I have shown that there are the forces present in the atoms, which represent the factor which determine the kind of crystals they form. Elements forming the same kind of crystals, having similar forces, appear to have similar biological properties. By applying this view, I have found that, in general, from all the previously mentioned elements, only Hg, Bi, As, B, Sb and Sm have the same rhombohedral crystal form. In fact, all these rhombohedral elements, although of different series and periods have common biological properties: they are all anabolic. More importantly, the Hg, Bi, As and B have special antiseptic properties. Hg, Bi and As were the only elements which, for years, were used for the treatment of spirochetoses and more specifically, for treatment of syphilis. Also, As, Sb and Bi are members of the same very active anabolic series, the 6A.

Furthermore, Bi represents also the anabolic element with the highest atomic weight, respectively acting at the lowest level of the organization. All these are making from the elements of the rhombohedral group of Bi, Hg, As, B, Sb and Sm, very highly interesting elements for special activities, such as antiviral and especially as anabolic agents at the lowest subnuclear level.

In the therapeutic study of these agents, I have found as a capital character that they should have lipidic properties, that is, to be more soluble in neutral organic solvents than in water. This allows the agents to be specifically taken up by the abnormal formation in the subject, which formation is rich in free lipids. The study of the activity of the different compounds of these important elements has shown the capital importance of this fundamental lipidic character. Some salts of the elements having a lipidic fatty acid component, such as, for example, oleate, palmitate, or the like, have not shown the desired effects. I explained this through the fact that the element as a cation in the compound is easily separated and bound to other nonlipidic anions. I resolved this problem by having the element directly incorporated into the nonpolar group of a lipidic substance. I made this especially by incorporating the element in the nonpolar part of the fatty acids at their double bonds.

In the following method, the element as such or in the form of a salt which is easily dissociated, is mixed with an oil or with its fatty acids or other unsaturated lipids, especially the polyunsaturated lipids. The mixture is heated to a temperature at which the dissociated element is attached to the lipid at their double bonds which, were previously bound to oxygen and which I found to open at this high temperature. The combination between the element and the double bond corresponds to an exothermic reaction. The heating is stopped at this moment with the result of the element incorporated in the nonpolar part of the fatty acids.

I have incorporated the elements of this rhombohedral group predilectly in vegetable oils such as sesame or safflower oil or its fatty acids. The problem of what compound has to be used has appeared capital for a good and sufficient incorporation of the element. The use of the element as such or other compounds has given insufficient results. I found that organic acid salts of these elements provide the best results. Thus, 5% by weight of bismuth oleate mixed with sesame oil is heated at around 300 DEG C. under constant stirring for a sufficient time in order to obtain a good incorporation.

The allylically unsaturated compound is preferably a naturally occurring oil containing polyunsaturated fatty ester, such as an animal, vegetable, or fish oil, and, particularly, polyunsaturated vegetable oils. Sesame oil, a vegetable oil consisting largely of triglycerides, is the most advantageous composition found to date in the practice of this invention.

The composition utilized should contain a significant percentage of molecular species having allylic moieties to render the compositions useful according to the invention. Such moieties are indicated by the following partial structures --CH.dbd.CH--CH2 --CH.dbd.CH--and/or --CH.dbd.CH--CH.dbd.CH--CH2 --. As indicated, the unsaturation can be conjugated or nonconjugated, but the composition must contain allylic methylene hydrogen.

Such compositions may initially be oxidized or heated in the presence of air or oxygen at the temperature range between about 100 and about 150 DEG C. The oxygen can be obtained by merely heating the composition in a vessel which is open to the atmosphere, but preferably and advantageously, the source of oxygen is a gas such as air which is injected into the heated oil. Introduction of air also provides a source of agitation.

The heating step is conducted for a period of from about 15 minutes to about three hours. The temperature should be maintained at an upper limit within the range of above about 260 DEG to 325 DEG C. and preferably about 280 DEG to 300 DEG C. These temperature limitations are based on a heating time of about one-half hour. The temperatures can be altered within limits depending on the time of heating. For example, when the temperature is about 265 DEG C., the time is about one-half hour, while temperature as high as 300 DEG C. require a shorter period of time for heating. Higher temperatures for a prolonged period of time tend to degrade the composition and should thus be avoided.

Agitation, by stirring for example, aids in the reaction, and experiments to date indicate that a fairly vigorous stirring is advantageous. The introduction of air into the mixture during the heating is also very advantageous, particularly when the mixture is not subjected to prolonged heating and thus, is the preferred method. The mixing or stirring can be accomplished with the introduction of the air. After the reaction has taken place, the mixture is cooled. The remaining fluid is ready for use after appropriate sterilization for injection or incorporated into capsules, such as gelatin, for oral administration.

The precise nature of the compositions which result from the above-described treatment or the identity of the effective component or components is not presently known. It is known, however, that these compositions do include the range of about 0.1 to 10% weight percent has been found to be effective.

As mentioned above, although any organic salt can be used, including carbonate, acetate, or the like with the element bonding the fatty acids present in the oil. Although any amount above 0.1% of the element incorporated into the composition is useful, the preferred amount ranges between about 0.5 to 10, and most preferably about 5, weight percent.

The so obtained incorporated product is used for oral administration, and after sterilization, for intramuscular injections. The incorporated element have a very low toxicity with no undesired side effects. A certain pharmacological activity is found in all the compounds of the rhombohedral elements in general. More accentuated are their lipidic compounds. Especially active, however, are the bismuth and mercury compounds incorporated alone or in combination in oils, in their fatty acids or in other different agents with lipidic properties.

In the pharmacological activity of lipidic rhombohedral elements and especially of the incorporated bismuth or mercury, several actions are recognized. In one, the anabolic bismuth or mercury lipidic compound acts again the catabolic imbalance present as such, that is, reducing or even fully controlling this imbalance. This is very manifest for severe pain, controlled in less than an hour, by an oral intake of very small amounts of the incorporated bismuth or mercury compound, such as corresponding to 0.2-0.5 mg per dose. For intramuscular injection, a preferred daily dosage of between 0.5 to 10 cc per dose, administered once or twice daily, has been found to be generally effective, although additional doses could be administered for extreme situations. As such, the incorporated rhombohedral elements are working on many different conditions.

These analyses and clinical manifestations have to be changed by the administration of the incorporated compound. In a 5% preparation, amounts from about 0.5 to 10 cc daily are predilectly used for the treatment of catabolic imbalance. Other concentrations of agents can be converted to other doses containing the same or similar amount of active ingredient (i.e., the incorporated compound). In general, the higher the dose used, the better are the clinical

results.

Bismuth and the other elements of the group incorporated act thus upon other catabolic symptoms. Frank are the changes in the subjective manifestations of the neoplastic diseases, especially pain, difficulties in breathing and others. This applies also to the clinical manifestations of AIDS with characteristic catabolic imbalances, which manifestations are often fully controlled in a short time.

In another action, especially with higher doses the anabolic compounds and especially the bismuth or mercury incorporated compounds are inducing by themselves an anabolic imbalance. As this imbalance is not sterolic, it does not have the noxious effects of the usual sterolic imbalances. I have found that the presence of a nonsterolic anabolic imbalance is reducing the amount of sterols in the body. This is especially important for the neoplastic lesions, which are in general developing only with a sterolic imbalance. Consequently, especially the incorporated bismuth or mercury have through the nonsterolic anabolic exaggerated imbalance a special action also upon the anabolic lesions of the neoplastic diseases as well as other conditions. The direct anticatabolic action and the special exaggerated anabolic nonsterolic imbalance induced are leading to the destruction of such neoplastic lesions. Such organic changes were seen also in other conditions. Large lymphatic glands and the Kaposi lesions in AIDS have been reduced even after relatively a short treatment.

Another very important action is this of Bi and Hg, due to the fact that they are part of the elements of the 6th period, elements acting predominantly upon the subnuclear level. They act especially also upon the independent entities corresponding to this level, i.e., the viruses. With a treatment for some longer time and insufficiently high doses, it is expected to obtain a control of such viral diseases.

It was found that the treatment with incorporated rhombohedral elements has to be continued for sufficient time in adequate high amounts in order to obtain the desired results, i.e., other than the very impressive immediate effects on pain and other symptoms more especially.

Bismuth, mercury or arsenic can be used also in the different preparations, which were used especially for the treatment of syphilis. These agents of incorporated rhombohedral elements are used successfully together with other different agents, especially with those having anabolic properties, to enhance their anticatabolic action. They are also used with active catabolic agents, together or following their administration, in order to control exaggerated anabolic manifestations.

There are these different actions which are explaining the favorable effects obtained with the incorporated rhombohedral elements in a variety of pathological conditions, especially cancer, leukemias and viral conditions, mainly AIDS, herpes and Epstein-Barr disease.

There are these results already obtained and especially the multiple successful applications, which are making from the lipidic rhombohedral elements compounds in general and especially from the incorporated bismuth or mercury special valuable weapons in the fight against different diseases.

While it is apparent that the invention herein disclosed is well calculated to fulfill the objects above stated, it will be appreciated that numerous modifications and embodiments may be

devised by those skilled in the art, and it is intended that the append claims cover all such modifications and embodiments as fall within the true spirit and scope of the present invention.

Method of treating the clinical manifestations of viral diseases US4301150

The method of treating or alleviating the clinical manifestations of viral diseases which exhibit alkalosis which comprises administering to the host a non-toxic acidic salt of an inorganic acid.

SUMMARY OF THE INVENTION

A study of the clinical manifestations and analytical data of certain viral diseases, such as the common cold, have indicated that a dyschlorobiotic off-balance is present in the body. Local alkalosis of the nose and upper respiratory tract manifested by the rhinorrhea and tracheal and bronchial secretions exhibited by the common cold are apparently a consequence of this dyschlorobiosis. The secretions of the clinical manifestations of the common cold may have a pH as high as 8 to 8.5 depending on the severity of the cold.

This invention relates to an immediate means to combat these clinical manifestations of such viral diseases through the control of the alkalosis by administration to the body of acidifying compositions or compounds, such as non-toxic acidic salts of inorganic acids.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The non-toxic, water soluble acidic salts which can be used according to this invention include, without limitation, the ammonium salts of phosphoric acid, hydrochloric acid and sulfuric acid. Research to date has shown that mono-ammonium phosphate salt is considerably superior to other ammonium salts of inorganic acids. The mono-ammonium phosphate salt is also referred to as ammonium phosphate mono-basic. Ammonium phosphate hemi-basic is also included within the invention. The hemi-basic salt is strongly acid in reaction, while the mono-basic is mildly acid in reaction. Metal salts of the inorganic acids have not been found to be particularly effective, although some metal salts, particularly of an element of the first series of the Periodic Chart, such as lithium, potassium and cesium, could be used. Mixtures of the salts are also effective.

The inorganic acid ammonium salts of this invention are anti-pathogenic, and thus no claim is made that the acid ammonium salts act directly on or kill any virus or microorganism. Relief of the clinical manifestations or symptoms of the viral disease, however, relieves the body of a host defense function and thus aids the body's host defense system in attacking the virus in its normal manner, which may result in a faster cure than might normally be expected.

The amount of acidic inorganic salt administered is highly important. Little or no response is obtained when insufficient amounts are used. The exact amount to obtain relief of the symptoms of the viral disease will, of course, depend upon the particular symptoms and severity thereof exhibited by the person having the disease, the pH of the host, as well as the particular acidic inorganic salt being administered. Mildly acid salts will, of course, require

higher dosages than strong acid salts. Research to date indicates that a sufficient amount of the acid salt should be administered to obtain a urine pH below about 5.5. With respect to mono-ammonium phosphate, one gram administered orally and repeated every half hour until the symptoms are fully controlled is recommended as a general rule, and for severe symptoms, higher doses, even up to 3 grams every half hour, may be used. Sufficient amounts of the acidic inorganic salts should be given to at least effect neutralization of the alkalosis of the host.

A study of the use of the ammonium salts has shown a low toxicity (acute, subacute, as well as chronic). No side effects were observed except that in a few cases, symptoms of gastric acidity were observed, especially when using high doses. By taking food together with the preparation, this occurrence is highly reduced. The mono-ammonium phosphate and the ammonium phosphate hemi-basic have a very low toxicity. Both have been used in the preparation of foods and mono-ammonium phosphate has been used for many years as a food additive. The estimated LD/50 of mono-ammonium phosphate in humans, based on tests in mice, is about 280 grams.

The inorganic acidic salts can be administered in any conventional manner such as by injection, but oral administration in gelatin capsules is the recommended manner of administration.

Approximately 100 patients having the common cold and exhibiting the normal symptoms therefrom, including rhinorrhea and tracheal and bronchial secretions and local alkalosis of the nose and upper respiratory tract, were treated by oral administration of 1 to 3 grams of mono-ammonium phosphate encased in a water soluble gelatinous capsule every half hour. The majority of the patients exhibited normal cold symptoms and were given 1 gram of mono-ammonium phosphate every half hour and the remainder who exhibited rather severe symptoms were given between 2 and 3 grams every half hour. Approximately 85 of the patients exhibited marked improvement with practically complete control of the cold symptoms within about 24 to 48 hours.

Fifteen patients having herpes simplex were treated with mono-ammonium phosphate administered orally at 1 gram every half hour. All patients responded showing distinct improvement with blisters disappearing within about 24 to 48 hours. Approximately 8 patients responded within the first day of treatment. Left by itself, the blisters normally persist for one week or more.

One patient with herpes zoster was treated with mono-ammonium phosphate administered orally at 1 gram every half hour. The patient responded within about 48 hours with substantial disappearance of the lesions. The pain, however, particularly at night, persisted. This is not unusual, however, since in the normal cure by the body host defense system, the pain occasionally persists after evidence of the inflammation has subsided.

Eighteen rabbits were inoculated with smallpox vaccine in the normal manner. The rabbits were divided into two groups of 9. The first group was given drinking water containing 2% by weight of mono-ammonium phosphate. The second group was given drinking water containing only 2% by weight salt. Both groups drank the normal amount of water. Within 24 hours the second control group developed strong very red inflammation in the inoculated area while the group to which mono-ammonium phosphate was given developed only tiny pink or brown spots.

Method for relieving pain or producing analgesia with n-butanol US4756909

A method for treating a host for inducing relief of pain or anesthesia which comprises administering hydrolyzed epichlorohydrin, magnesium thiosulfate, or a butanol at the site of the painful area.

TECHNICAL FIELD

This invention relates to methods and preparations for relieving pain or producing analgesia.

BACKGROUND ART

A number of methods exist for treating pain: an example being U.S. Pat. No. 3,898,325. The applicant has found a new method which is particularly effective for this purpose in compositions which are relatively simple to prepare and administer.

SUMMARY OF THE INVENTION

It has now been found that by administering various agents, such as hydroyzed epichlorohydrin (i.e., 1-chloro-2,3-epoxy propane), magnesium thiosulfate, or n-butanol directly to the painful area of a host will relieve the pain or produce analgesia therein.

DESCRIPTION OF THE INVENTION

It is known that the manifestation of pain is observed at the so-called trigger points. To successfully treat such pain, the administration of the compounds of the invention, preferably by injection, is found to control the pain in the immediate area as well as in the entire affected region.

One embodiment of the invention relates to the injection of from 1 to 10 ml of a solution of between 0.1 and 1.5 weight percent hydrolyzed epichlorohydrin at the trigger point or immediate painful area. The epichlorohydrin can be hydrolyzed by heating it in water. These amounts have been found to be advantageous, but can be higher or lower if desired. For example, up to 50 ml of a 0.5 weight percent solution can been used for exceptionally severe cases.

Generally, the pain is relieved in minutes following the injection. If necessary, the injections may be repeated, preferably 1-2 days later. If a stronger pain is present the next day at the site of the injection, this may be the result of an local inflammatory reaction. When this occurs, the pain usually disappears the day after, and the long term results are generally better.

Another approach for relieving pain is based upon the fact that pain generally has either an acid or alkaline pattern. This character is recognized through a relationship with the urinary pH: the acid pain being stronger with a lower pH and being weaker with a higher pH. The alkaline pains is just the opposite.

The acid pain corresponds to an anabolic imbalance with the predominant pathogenic action caused by steroids, while the alkaline pain corresponds to a catabolic action, with the predominant pathogenic action caused by fatty acids.

Many different agents can be used to counteract these imbalances. For the anabolic imbalances which are evidenced by acid pain, the injection of a solution of magnesium thiosulfate is utilized. The amount of this solution includes between about 10 and 50 ml of a water solution containing between about 10 and 50 weight percent magnesium thiosulfate.

For alkaline pain, which indicates a catabolic imbalance, a solution of butanol in water is used. The amount of this solution ranges from 5 to 25 ml of a solution of between about 5 and 10 weight percent butanol in water. Either n-butanol or sec-butanol can be used, with n-butanol preferred for best results. It is preferable to add to the butanol solutions about 25 to 50 percent by weight (based on the amount of butanol) of coramine (niketamide) for even better results.

As with the hydrolyzed epichlorohydrin solution, these solutions are preferably administered by injection. If the type of pain cannot be characterized as acid or alkaline, then the epichlorohydrin solution should be administered. It is also possible to use mixtures of these solutions.

When the nature of the disease which is causing the pain is known, more special agents, which can treat the disease or the symptoms of the disease, can be added to these solutions. Also, the number of injections can be repeated to enhance the pain reducing effect.

The preparations of the invention have practically no toxicity in the doses used.

SELENIUM COMPOSITIONS FOR TREATMENT OF DISEASE
WO9003175

Bivalent negative selenium compositions of a red selenium/oil reaction product, methods of preparing such products, and methods for administering such products to patients to treat anabolic conditions.

Technical Field

The present invention concerns certain selenium compositions, methods for preparing such compositions, and methods for treating different conditions and diseases.

Summary of the Invention

The present invention relates to a method for preparing a bivalent negative selenium composition which comprises mixing gray selenium powder with an animal oil, vegetable oil, fish oil, or mixture thereof to form a suspension; heating the suspension to a sufficient temperature to form a red selenium/oil reaction product; and cooling the reaction product to recover a bivalent negative selenium composition containing between 0.1 and 2 weight percent red selenium.

Preferably, the suspension is heated to about 150 to 200"C for a sufficent time to form a red selenium composition having at least about 1 weight percent selenium in the oil, and the oil is tung oil.

The invention also relates to a method for preparing a bivalent negative selenium composition which comprises exothermically reacting selenium monochloride or selenium monobromide with an animal, vegetable or fish oil to form a red-selenium/oil reaction product containing between 0.1 and 2 weight percent selenium.. In this embodiment, preferred oils include sesame, safflower, tung, corn, sardine, cod liver, or salmon oil. This method further comprises adding an oxidant to the oil prior to adding the selenium compound, wherein the oxidant is a 3-ketone, preferably 3-pentanove or 3-heptanone.

The invention also relates to the red-selenium oil reaction products produced by these methods, along with methods for treating the effects of an anabolic condition in a patient which comprises administering to the patient a sufficient amount of one of these reaction products.

Specifically, this method treats the effects of an anabolic condition in a patient by administering to the patient a sufficient amount of a red-selenium/oil reaction product containing 0.1 to 5 weight percent selenium. In these methods, the amount of reaction product to be administered ranges from about one to 100 drops per dose, each dose administered between 2 and six times per day.

Description of the Invention

I have found that the bivalent negative selenium, in its different preparations, has a salutary effect, especially upon pathological conditions when they have an anabolic character.Such conditions are the neoplastic conditions, arthritis, arteriosclerosis, epilepsy, convulsions, arrythmia, mania, sclerosis, cyrrhosis, inconsolidated fractions, dermatoses, drug, alcohol, smoking, addiction, different viral infections, as AIDS, the common cold and others, and acid symptoms such as acid pain, itching, vertigo, dyspnea and impaired hearing.

I have found that good results are particularly obtained with the administration of a bivalent negative red selenium composition.

I have further found that especially active and with a minimal toxicity are the preparations in which the red selenium is a colloidal compound.

According to one embodiment of the. invention such a colloidal red selenium compound is obtained through an exothermic reaction resulting from mixing selenium monobromide or monochloride with an oil - or a preparation which has an oil or a material with a lipidic character in its constitution.

The product of the invention, colloidal red selenium compound, is used in suspensions having preferably the selenium from 0.18 to 5%. This proportion is not limitative.

In another form of the invention, red selenium is obtained by progressively heating a mixture of gray selenium powder and an oil, preferably tung oil, until the suspended selenium is changed into a red selenium. Agitating the mixture by strong stirring facilitates this reaction. The reaction product is evidenced by a reddish color. The mixture is then cooled and the red

selenium is incorporated in the fatty acid molecules.

By further heating of the mixture, an exothermic reaction rakes place resulting in an undesirable and nonuseful brown color reaction product.

I have found that the product of the first reddish color has a much stronger pharmacological action than the last brown incorporated product. These changes are still more manifest for the reddish color selenium incorporation in the tung oil, wherein the amount of incorporated selenium ranges from 0.1 to about 5% by weight.

The red selenium composition described above can be obtained with any compound having lipidic properties. Such lipidic products include any animal, vegetable or fish oil, and more particularly, oils of sesame, safflower, tung, corn, cod liver, sardine, salmon or other fish, suspensions or solutions of phospholipids or animal bodies or organs, such as thymus, intestines, spleen, liver or others, lecithins of eggs, soya beans, Bixa seeds, phospholipids of other plants fungi, especially of those used to produce antibiotics, microbes, milk, colostrum, aminoacids, alkaline and acid aminoacid, proteose, peptones, histones, nucleoproteins and others.

This enumeration is not limitative as to the material to which the red colloidal selenium is mixed, apporting its properties and consequently its use as applied to biological entities.

I have shown that these reaction products have a manifest antineoplastic action - when administered orally, even in small amounts.

As noted above, by mixing selenium monobromide or monochloride with an oil, an exothermic reaction takes place resulting in a red selenium colloidal compound. I have further found that by adding to the red colloidal compound an oxidant its action is enhanced. A good preparation is obtained by having the colloidal red selenium administered together with 3-ketones agents such as 3-pentanone and 3heptanone or with other oxidizing agents. I have found that as oily material the use of apreparation having equal amounts of 3-pentanone and/or 3-heptanone in an oil, results in a specially active antineoplastic preparation for the mixture with the selenium monobromide or monochloride.

According to the invention, the selenium monobromide or monochloride is mixed with a lipidic preparation, preferably having an oil or a fatty acid compound in its constitution.

Especially good preparations are obtained by mixing the selenium monobromide or nonochloride with tung oil, safflower or fish oils or their fatty acids. In the different mixtures, the selenium monobromide or nonochloride is added in a proportion so as to result in a selenium/oil reaction product containing between 0.1 % to 5% percent red selenium.

The products of the invention are administered orally or by injections in repeated doses preferably between 2 and six, - most preferably four times per day, each dose containing between from one drop and 100 drops (5 ml) according to the concentration of the selenium in the oil and of the specific condition to be treated.

No toxic effects or side effects are seen, the products of the invention being particularly well tolerated by patients.

The preparation of the invention due to the action of bivalent negative selenium as part of a lipid and of the fatty acids proper to the tung oil has a manifest antianabolic action. Thus, it is useful for treating the effects of anabolic conditions, such as alcohol, smoking or drug addiction. It has also shown special favorable effects, both subjective and objective, upon various neoplastic conditions.

The products of the invention are administered orally or by injections, preferably intramuscularly or into the lesion itself. Very characteristic, favorable subjective effects as on pain are in general obtained in very short time, indicating a more rapid action which was not seen with other selenium compounds. The same, the objective changes are obtained also in special short time.

The experimental and clinical research have thus shown the exceptional therapeutic value of the red selenium and especially of its colloidal form - with a very low toxicity, especially in the minimal amounts necessary. It appears rapidly absorbed and consequently active even in the exceptional small amounts used.

As the subjective and objective effects upon the neoplastic diseases are generally seen even with very little amounts, and within a short time, the method represents an important progress in the treatment of these conditions.

SELENIUM COMPOSITIONS FOR TREATMENT OF DISEASE WO9003175

Bivalent negative selenium compositions of a red selenium/oil reaction product, methods of preparing such products, and methods for administering such products to patients to treat anabolic conditions.

Technical Field

The present invention concerns certain selenium compositions, methods for preparing such compositions, and methods for treating different conditions and diseases.

Summary of the Invention

The present invention relates to a method for preparing a bivalent negative selenium composition which comprises mixing gray selenium powder with an animal oil, vegetable oil, fish oil, or mixture thereof to form a suspension; heating the suspension to a sufficient temperature to form a red selenium/oil reaction product; and cooling the reaction product to recover a bivalent negative selenium composition containing between 0.1 and 2 weight percent red selenium.

Preferably, the suspension is heated to about 150 to 200"C for a sufficent time to form a red selenium composition having at least about 1 weight percent selenium in the oil, and the oil is tung oil.

The invention also relates to a method for preparing a bivalent negative selenium composition which comprises exothermically reacting selenium monochloride or selenium

monobromide with an animal, vegetable or fish oil to form a red-selenium/oil reaction product containing between 0.1 and 2 weight percent selenium.. In this embodiment, preferred oils include sesame, sa-fflower, tung, corn, sardine, cod liver, or salmon oil. This method further comprises adding an oxidant to the oil prior to adding the selenium compound, wherein the oxidant is a 3-ketone, preferably 3-pentanove or 3-heptanone.

The invention also relates to the red-selenium oil reaction products produced by these methods, along with methods for treating the effects of an anabolic condition in a patient which comprises administering to the patient a sufficient amount of one of these reaction products.

Specifically, this method treats the effects of an anabolic condition in a patient by administering to the patient a sufficient amount of a red-selenium/oil reaction product containing 0.1 to 5 weight percent selenium. In these methods, the amount of reaction product to be administered ranges from about one to 100 drops per dose, each dose administered between 2 and six times per day.

Description of the Invention

I have found that the bivalent negative selenium, in its different preparations, has a salutary effect, especially upon pathological conditions when they have an anabolic character.Such conditions are the neoplastic conditions, arthritis, arteriosclerosis, epilepsy, convulsions, arrythmia, mania, sclerosis, cyrrhosis, inconsolidated fractions, dermatoses, drug, alcohol, smoking, addiction, different viral infections, as AIDS, the common cold and others, and acid symptoms such as acid pain, itching, vertigo, dyspnea and impaired hearing.

I have found that good results are particularly obtained with the administration of a bivalent negative red selenium composition.

I have further found that especially active and with a minimal toxicity are the preparations in which the red selenium is a colloidal compound.

According to one embodiment of the. invention such a colloidal red selenium compound is obtained through an exothermic reaction resulting from mixing selenium monobromide or monochloride with an oil - or a preparation which has an oil or a material with a lipidic character in its constitution.

The product of the invention, colloidal red selenium compound, is used in suspensions having preferably the selenium from 0.18 to 5%. This proportion is not limitative.

In another form of the invention, red selenium is obtained by progressively heating a mixture of gray selenium powder and an oil, preferably tung oil, until the suspended selenium is changed into a red selenium. Agitating the mixture by strong stirring facilitates this reaction. The reaction product is evidenced by a reddish color. The mixture is then cooled and the red selenium is incorporated in the fatty acid molecules.

By further heating of the mixture, an exothermic reaction rakes place resulting in an undesirable and nonuseful brown color reaction product.

I have found that the product of the first reddish color has a much stronger pharmacological

action than the last brown incorporated product. These changes are still more manifest for the reddish color selenium incorporation in the tung oil, wherein the amount of incorporated selenium ranges from 0.1 to about 5% by weight.

The red selenium composition described above can be obtained with any compound having lipidic properties. Such lipidic products include any animal, vegetable or fish oil, and more particularly, oils of sesame, safflower, tung, corn, cod liver, sardine, salmon or other fish, suspensions or solutions of phospholipids or animal bodies or organs, such as thymus, intestines, spleen, liver or others, lecithins of eggs, soya beans, Bixa seeds, phospholipids of other plants fungi, especially of those used to produce antibiotics, microbes, milk, colostrum, aminoacids, alkaline and acid aminoacid, proteose, peptones, histones, nucleoproteins and others.

This enumeration is not limitative as to the material to which the red colloidal selenium is mixed, apporting its properties and consequently its use as applied to biological entities.

I have shown that these reaction products have a manifest antineoplastic action - when administered orally, even in small amounts.

As noted above, by mixing selenium monobromide or monochloride with an oil, an exothermic reaction takes place resulting in a red selenium colloidal compound. I have further found that by adding to the red colloidal compound an oxidant its action is enhanced. A good preparation is obtained by having the colloidal red selenium administered together with 3-ketones agents such as 3-pentanone and 3heptanone or with other oxidizing agents. I have found that as oily material the use of apreparation having equal amounts of 3-pentanone and/or 3-heptanone in an oil, results in a specially active antineoplastic preparation for the mixture with the selenium monobromide or monochloride.

According to the invention, the selenium monobromide or monochloride is mixed with a lipidic preparation, preferably having an oil or a fatty acid compound in its constitution.

Especially good preparations are obtained by mixing the selenium monobromide or nonochloride with tung oil, safflower or fish oils or their fatty acids. In the different mixtures, the selenium monobromide or nonochloride is added in a proportion so as to result in a selenium/oil reaction product containing between 0.1 % to 5% percent red selenium.

The products of the invention are administered orally or by injections in repeated doses preferably between 2 and six, - most preferably four times per day, each dose containing between from one drop and 100 drops (5 ml) according to the concentration of the selenium in the oil and of the specific condition to be treated.

No toxic effects or side effects are seen, the products of the invention being particularly well tolerated by patients.

The preparation of the invention due to the action of bivalent negative selenium as part of a lipid and of the fatty acids proper to the tung oil has a manifest antianabolic action. Thus, it is useful for treating the effects of anabolic conditions, such as alcohol, smoking or drug addiction. It has also shown special favorable effects, both subjective and objective, upon various neoplastic conditions.

The products of the invention are administered orally or by injections, preferably intramuscularly or into the lesion itself. Very characteristic, favorable subjective effects as on pain are in general obtained in very short time, indicating a more rapid action which was not seen with other selenium compounds. The same, the objective changes are obtained also in special short time.

The experimental and clinical research have thus shown the exceptional therapeutic value of the red selenium and especially of its colloidal form - with a very low toxicity, especially in the minimal amounts necessary. It appears rapidly absorbed and consequently active even in the exceptional small amounts used.

As the subjective and objective effects upon the neoplastic diseases are generally seen even with very little amounts, and within a short time, the method represents an important progress in the treatment of these conditions.

COMPOSITION AND METHOD FOR TREATMENT OF COPPER DEFICIENCY
WO8900040

A method for making a composition containing a fatty acid or fatty ester compound and copper. The compositions produced by the method. Administration of these compositions to a patient to increase the copper content of cells or tissue having a copper deficiency or to treat at least some of the symptoms of diseases or adverse effects caused by this copper deficiency.

Background

It is known that the abnormal cells in general and the neoplastic cells in particular are poor in copper, a fact which is considered as including and enhancing their abnormal character. It is also known that the blood plasma of subjects with such abnormal conditions is especially rich in copper, apparently due to the body's attempt to correct the cellular copper deficiency. The form under which the copper is circulating in the blood, that is, mainly as ceruloplasmin, however, is not the proper form from which the copper can be taken by the abnormal cells.

Summary of the Invention

The invention comprises novel compositions of fatty acids, ester, or oils which include copper incorporated therein. These composition are made by heating the oil component to a temperature of at least above 230 C for a sufficient time to incorporate a predetermined amount of copper into the oil. At least about 0.1% can be used, although between 1 and 10% is preferred.

These compositions of the invention may be administered to a patient who has cells or tissue which are deficient in copper to increase the copper content as well as to treat the symptoms of diseases or adverse effects caused by the copper deficient cells or tissue.

Detailed Description of the Invention

I have found that in general, the abnormal cells and tissues in the body have free lipids. Thus, a lipid or compound having a lipidic character introduced into the body can be selectively taken by the abnormal cells. Accordingly, it is believed that a copper compound having lipidic properties is useful as a therapeutic agent for patients who have such abnormal cells.

I have found that copper can be incorporated in the molecule of a fatty acid by heating together an organic or inorganic salt of copper with a fatty acid or its oil.

Preferably, the fatty acid or oil is previously oxidized by being heated and mixed with air or oxygen. The mixtures of copper and fatty acids or oil are heated at a temperature above about 2300C for a time until an exothermic reaction is observed, which reaction indicates that the incorporation is taking place.

Examples of the copper/fatty acid or oil compositions that can be used according to the invention include the reaction products of allylic unsaturated fatty acids or esters and a copper salt. These reaction products are produced by heating a liquid composition containing a fatty acid or fatty ester, structurally characterized by allylic unsaturation with a copper salt. Applicant believes that any copper salt is suitable for this invention. Preferably, the copper salt is an organic copper salt such as cupric acetate, and the liquid is preferably oxidized for example, by bubbling air or oxygen through the reaction mixture.

The allylically unsaturated compound is preferably a naturally occurring oil containing polyunsturated fatty'esters, such as an animal, vegetable, or fish oil, and, particularly, polyunsaturated vegetable oils. Sesame oil, a vegetable oil consisting largely of triglycerides, is the most advantageous composition found to date in the practice of this invention.

The composition utilized should contain a significant percentage of molecular species having allylic moieties to render the compositions useful according to the invention.

Such moieties are indicated by the following partial structures -CH=CH-CH2-CH=CH- and/or -CH=CH-CH=CH-CH2-, As indicated, the unsaturation can be conjugated or nonconjugated, but the composition must contain allylic methylene hydrogen.

Such compositions may initially be oxidized or heated in the presence of air or oxygen at the temperature range between about 1000C and about 1500C. The oxygen can be obtained by merely heating the composition in a vessel which is open to the atmosphere, but preferably and advantageously, the source of oxygen is a gas such as air which is injected into the heated oil. Introduction of air also provides a source of agitation.

The heating step is conducted for a period of from about 15 minutes to about two hours. The temperature should be maintained at an upper limit within the range of about 2300C to 2500C, and preferably about 2350C to 2400C. These temperature limitations are based on a heating time of about one-half hour.

The temperatures can be altered within limits depending on the time of heating For example, when the temperature is about 235 C, the time is about one-half hour, while temperatures as high as 2500C require a shorter period of time for heating.

Higher temperatures for a prolonged period of time tend to degrade the composition and should thus be avoided.

Agitation, by stirring for example, aids in the reaction, and experiments to date indicate that a fairly violent stirring is advantageous. The introduction of air into the mixture during the heating is also very advantageous, particularly when the mixture is not subjected to prolonged heating and thus, is the preferred method. The mixing or stirring can be accomplished with the introduction of the air.

After the reaction has taken place, the mixture is cooled. The remaining fluid is ready for use after appropriate sterilization for injection or incorporated into capsules, such as gelatin, for oral administration.

The precise nature of the compositions which result from the above-described treatment or the identity of the effective component or components is not presently known. It is known, however, that these compositions do include copper and that a proportion of copper in the range of about 1 to 10 weight percent has been found to be effective.

As mentioned above, although any copper salt may be used, an organic salt of copper, such as cupric acetate, is preferred, with the copper bonding the eleostearic acid present in this oil. Although any amount above 0.1% of copper incorporated into the composition is useful, the preferred amount ranges between about 1 to 10 weight percent.

The products obtained have the copper incorporated in general at the level of the double bonds of the different unsaturated fatty acids, this causes their toxicity to be exceptionally low. The injection of 1 ml of a product having 5% copper to a mouse does not kill it.

The incorporated copper composition may be administered orally, by injections, sublingually or rectally in the appropriate formulation.

The incorporated copper is believed to be absorbed by the abnormal cells, thus compensating for their low copper content. This treatment produces objective and subjective improvement in the conditions, of patients having a variety of diseases based upon such abnormal cells. The neoplastic diseases are examples of diseased in which low cellular copper abnormal cells are found.

Such low cellular copper abnormal cells are believed cause an anabolic imbalance in the body. This anabolic imbalance can be analyzed and diagnosed by blood and urine analyses. An eosinophilia (above 100/cmm), a low red cell sedimentation rate (below 15 ml/l hour), a low serum potassium (below 4.5 mEq), a urinary alkaline pH (above 7), low specific gravity (below 1.016), high surface tension (above 89 dynes/cm), and high calcium or chloride excretion are indications of an anabolic imbalance. (The opposite analyses would indicate a catabolic imbalance.)

These analyses and clinical manifestations have to be changed by the administration of the incorporated copper compound. In a 5% copper incorporated preparation, amounts from about 2 to 10 ml daily are predilectly used for the treatment of this anabolic imbalance.For the neoplastic conditions with catabolic imbalances, low doses from 1/10 to 2 ml daily are predilectly used. In general the higher the dose used, the better are the clinical results.

Interesting results are those concerning pain, the changes induced in the lesions manifesting first an action upon pain. Manifest changes in the tumors and in the subjective manifestations of the neoplastic diseases are obtained even in a very short time. Thus, the incorporated

copper appears as a predilect treatment of the symptoms of neoplastic conditions, and possibly to the treatment of such condition themselves.

Good results were also obtained in the use of the incorporated copper compounds for the different manifestations of AIDS (acquired immune deficiency syndrome) as well as for the ARC (AIDS related complex).

Interesting also are the results in almost all the different conditions, such as neurological conditions, epilepsy and others, the problem of cellular copper deficiency being a general pathological occurrence. Interesting is the action of the lipidic copper products on the viral infections.

The incorporated copper composition may be administered together with different other agents.

PROCEDIMIENTO PARA PRODUCIR COMPUESTOS ORGANICOS DE SELENIO
MX155315

COMPOSIZIONE FARMACEUTICA AD ATTIVITA' ANTIEMORRAGICA
IT1152378

Treating alcoholism or alcoholic intoxication
IT1152302

COMPOSIZIONE FARMACEUTICA CONTRO LA STANCHEZZA
IT1152292

COMPOSIZIONE FARMACEUTICA AD ATTIVITA' ANTIEMICRANICA
IT1157291

COMPOSIZIONE FARMACEUTICA AD ATTIVITA' ANTIULCERA
IT1155354

COMPOSIZIONE FARMACEUTICA AD ATTIVITA' ANTIARTRITICA
IT1155353

COMPOSIZIONI FARMACEUTICHE AD ATTIVITA' ANTINEOPLASTICA
IT1151780

COMPOSIZIONI FARMACEUTICHE AD ATTIVITA' ANTINEOPLASTICA
IT1151779

Metallic selenium heated with eleostearic acid or tung oil
IT1164188

COMPOSIZIONI FARMACEUTICHE E DIETETICHE AD ATTIVITA' IPOCOLESTEROLEMICA
IT1173460

COMPOSIZIONE AD ATTIVITA' ATABAGICA
IT1161212

Agents against alcoholism and alcohol intoxication - produced by oxidising allylically unsaturated fatty acid(s) and ester(s) to increase peroxide titre
DE2741698

MITTEL ZUR BESEITIGUNG ODER VERMINDERUNG DES RAUCHVERLANGENS BEIM MENSCHEN
DE2642668

Anti-alcoholism agents contg sulphurized polyunsaturated oils - and pref contg free sulphur which continues to react with the oils
DE2510038

MITTEL ZUR BEHANDLUNG VON SUCHT UND ALKOHOLISMUS
DE2302371

Process for the preparation of a product mixture comprising sulphurised, polyunsaturated fatty acids or triglycerides
CH631896

THERAPEUTIC COMPOSITION CONTAINING MEMBERS OF HEXANEHEXOLS AND DISACHARIDES
CA884276

COMPOSITION AND METHOD FOR TREATMENT OF COPPER DEFICIENCY
AU7696187

ELIMINATING OR REDUCING THE DESIRE FOR SMOKING
AU1800876

ORGANISCHE SELENVERBINDUNGEN MIT NEOPLASTISCHER AKTIVITAET.
AT17236

PHARMACEUTICAL COMPOSITIONS CONTAINING AT LEAST ONE POLYFLUORINATED ALCOHOL
NZ20439
