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Clinical trial of dimethyl sulfoxide (DMSO) on sixteen patients with chronic arthritis

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CLINICAL TRIAL OF DIMETHYL SULFOXIDE (DMSO) ON SIXTEEN PATIENTS WITH CHRONIC ARTHRITIS

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PREFACE

My decision to choose dimethyl sulfoxide as the topic for my senior thesis was based partially on my own curiosity concerning the widespread interest in the potentialities of the drug and secondly the availability of the drug for experimental purposes. My purpose has been to present the results of my clinical investi-gations using the drug on patients suffering from chronic arth-ritic disorders, with a brief resume of the literature *to* date including such aspects as the history, chemistry, pharmacology, toxicity, side effects, and therapeutic usage of the drug. This study was terminated in November, 1965, because the Food and Drug Administration withdrew the drug from clinical trials because of reports of toxicity to the lens of animals.

My studies *at* the University Arthritis Clinic are incomplete because of this unfortunate circumstance, and I was compelled to request return of unused samples of DMSO from several patients who had just begun treatments and was unable to carry out my intention to expand my series and study long-range effects of DMSO. I believe, however, that the results I have obtained in the small series to be presented are fairly consistent and signif-icant in their own right.

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I. LITERATURE REVIEW

A. HISTORY

Dimethyl sulfoxide (DMSO) is an extraordinary chemical, a derivative of lignin, synthesized in 1867 by Saytzeff.[8] Today, it is mainly obtained as a by-product in the manufacturing of paper. Its industrial applications are numerous and diverse; it is used (1) as a solvent for resins, fungicides, dyes, pigments, etc. (2) as a reactant for chemical synthesis (3) as an extractant and (4) as a reaction medium to accelerate rates of chemical combination.

The medical community has been greatly interested in the extraordinary therapeutic reports by Jacob and his co-workers at the University of Oregon. In the lay press, the therapeutic promises of DMSO have merited the sobriquet "miracle drug." Early studies on DMSO followed a chance observation in 1964 at the research laboratories of Crown Zellerback Corp. in Camas, Washington, that DMSO carried toxic compounds through the skin and produced a systemic effect.[4] An experimental program was subsequently designed and carried out at the laboratories of the University of Oregon Medical School in Portland. Animal experiments showed that application of DMSO on third degree burns of rats resulted in an extension of the survival time and increased healing tendency. Accidentally, it was also shown that for chemical burns, pain can be reduced and the tendency for healing increased. Subsequently,

it was observed by John[5] that the external application in the case of hematomas, contusions, and tearing of muscles and ligaments of laboratory personnel resulted in some cases in a dramatic decrease of pain and swelling, an increase of mobility, and enhanced healing. The significance of these empirical observations was obvious. These early observations stimulated investigations at research centers throughout the world.

B. CHEMISTRY

Dimethyl sulfoxide (DMSO) $CH_3-\overset{\overset{O}{\|}}{S}-CH_3$ is a clear, colorless liquid of slight smell and low volatility (boiling point at 760 mn Hg = 189° C); vapor pressure at 20° C = 0.37 mn Hg; specific gravity at 20° C = 1.100. The substance blends well with water and the common solvents and is obtained commercially by oxidation of dimethyl sulfide. Chemically, DMSO is generally considered stable. Neither hydrogen nor carbon monoxide nor a combination of the two, in the absence of a catalyst, will reduce DMSO at 100° C and a pressure of 10 atmospheres. DMSO appears to be stable in pure oxygen at temperatures up to 150° C. DMSO is a versatile and powerful solvent that will dissolve most aromatic and unsaturated hydrocarbons, organic nitrogen compounds, organosulfur compounds and many inorganic salts. It is miscible with most of the common organic solvents such as alcohols, ketones, lower ethers, chlorinated solvents and aromatics.

C. PHARMACOLOGY

1. Anti-inflammatory Activity

DMSO in the laboratory shows anti-inflammatory activity against the Baker's yeast granuloma in guinea pigs and the carregeenin granuloma in rats. One such experiment reported in the brochure of the Merck, Sharp and Dohme Research Laboratories[8] involved the injection of an irritant (phlogistic agent) into the soft tissues of the plantar surface of the hindpaw of a rat which induced swelling of the entire paw. This edema could then be inhibited by anti-inflammatory drugs, either steroid or non-steroid. The effect of the anti-inflammatory drug was calculated as the per cent inhibition of edema formation in the foot. The results of the experiment indicated that little could be expected in the way of effects of DMSO when orally administered but when percutaneously administered, a significant degree of inhibition of carrageenin-induced edema in the foot was obtained. However, these experimenters felt that the possibility of an indirect mode of action rather than anti-inflammatory activity of the compound per se, could not definitely be ruled out.

2. Histamine Liberation by DMSO

A recent report by Kligman[7] indicates that DMSO possesses potent histamine-liberating properties at the site of application.

Using concentrations of DMSO at 70 per cent and greater on the backs of white and Negro subjects, almost invariably a solid, tense wheal was formed which is the classical cutaneous expression of histamine release. He also was able to show that the circulating basophils are decreased after extensive topical use. It has been shown that histamine-releasing drugs do have similar effects. He also notes that it would be wise to keep in mind, while treating patients with various disease states, some of whom may have unusual susceptibility, the possibility of histamine-mediated shock-like syndromes. He feels that DMSO is a potent vasodilator and will tend to pool blood in the peripheral circulation.

3. Analgesic Activity

Jacob showed that DMSO, in the laboratory, blocks conduction in an isolated nerve when a 25 per cent concentration is employed.[3] Conduction returns when the fiber is washed free of DMSO. This blockade may be an osmotic effect. Some analgesic activity has also been demonstrated when the reaction threshold is determined in an inflamed, swollen foot of the rodent. DMSO applied to the skin and back of the neck raises the squeak threshold in the inflamed area but not in the non-inflamed region. These results are believed consistent with the supposition that DMSO is absorbed through the skin and concentrated at the site of inflammation where it produces a peripheral analgesic effect perhaps by depressing the

conduction of afferent nerve impulses from the inflamed area.

4. Percutaneous Absorption of Drugs Dissolved in DMSO

Stoughton and Fritsch[15] showed that DMSO enhanced the percutaneous absorption through human skin of hexopyrronium bromide by at least a factor of 25 and fluocinolone acetonide by a factor of 5 fold. Kligman[6] reported that concentrated solutions of DMSO, 70 per cent and above, markedly increase the penetration of various dyes, steroids, and antiperspirants. The enhancement of penetration is not dependent on irreversible damage to the horny layer. A damage serious enough to allow complete penetration of the dye could not be repaired in a dead structure within a few hours. It can be inferred from a variety of observations that DMSO itself enters the skin with great speed. Its potentiating effect is realizable only so long as a critical quantity remains within the horny layer. It somehow creates pathways for the diffusion of a great variety of polar and non-polar substances.

5. Antibacterial and Antifungal Effects of DMSO

Herschler and Jacob[2] reported that aqueous solution strength at 35 per cent and higher has been found to be self-sterilizing. Tests organisms included: S. aureus, S. albus, E. coli, P. aeruginosa, A. aerogenes, B. subtilis, and spores of Mucor. Bacteriostasis, as expected, occurs at lower concentrations. However, Kligman's [7]

experiments revealed that DMSO, by modern standards, was only weakly antibacterial. He said it was roughly comparable to many other solvents and far inferior to alcohol. He also concluded that DMSO was a weak antifungal agent, but that it was a promising vehicle for antifungal agents in the treatment of ringworm infections.

6. Dissolution of Collagen

Scherbel, Mc Cormack and Poppo[13] have demonstrated in skin biopsies taken before treatment with DMSO and at three weekly intervals in patients with scleroderma that there is a slow dissolution of collagen in the scleroderma skin with eventual gradual disappearance of acid mucopolysaccharide while the elastic fibers remain intact. It is not known whether DMSO initiates destruction and eventual disappearance of the abnormal collagen or whether the DMSO merely increases cellular permeability and allows for the release of proteolytic enzymes. It is suggestive that the biochemical reaction responsible for the histologic change is selective for collagen.

7. Autonomic and Cardiovascular Actions

The Merck, Sharp and Dohme brochure[8] reports that tests in vagotomized anesthetized dogs indicated that intravenous DMSO in doses of 0.5 or 1 ml/kg has little or no atropine-like, ganglionic

blocking or other autonomic activities nor did the compound have significant effects on respiration, blood pressure, or electrocardiogram, except for a transient minor depressor effect followed by a slight pressor response.

D. TOXICITY

1. Summary of Toxicological Studies in Animals

Experiments carried out by Crown Zellerback Corporation[1] included application of DMSO to the skin of rabbits in single and repeated dosage. There was no evidence of irritation in either case and no gross or microscopic pathology. Allergenicity tests were also performed using guinea pigs injected with sensitizing doses of DMSO, and these were also negative. Other investigations on rats and mice by Sommer and Tamberger[14] indicate that undiluted DMSO or aqueous solutions of DMSO when administered orally or subcutaneously caused toxic symptoms only in large dosages. These symptons - numbness, analgesic, and respiratory troubles - were not characteristic, leading to the assumption that the central nervous system was affected and the vegetative nerve centers were restrained. The hygroscopic and consequently also osmotically effective properties explain at least partly the local DMSO effects on the skin and on mucous membrane. It has also been shown by Willson, Brown and Timmens[16] in their experiments that DMSO seems to have a relatively low order of systemic toxicity.

The acute oral and intravenous toxicity of DMSO was determined in mice and rats. Anemia and peritoneal inflammation were the main complications noted when rats were given intraperitoneal injections. In addition, a reversible hemolytic anemia was noted in dogs that received repeated intravenous injections of DMSO.

2. Summary of Toxicological Studies in Humans

The studies performed by Kligman[7] on human subjects substantiated the low-order animal toxicity of DMSO. In his investigations of the effect of chronic exposure to DMSO, nine ml. of 90 per cent DMSO were applied to the entire trunk, from the chin to the pelvic girdle, of 20 men daily for a period of 26 weeks. At 0, 2, 4, 8, 12, 16, and 24 weeks, the following lab studies were performed: complete blood count, urinalysis, thymol turbidity test, and serum glutamic oxaloacetic transaminase, sodium sulfobromophthalein, fasting blood sugar, and blood urea nitrogen determinations.

The subjects were examined and questioned weekly for one month and monthly thereafter. The occasional systemic symptoms which appeared during this six-month period were judged not to be drug dependent, because they were transient and varied from subject to subject. Most subjects did experience the disagreeable oyster-like breath odor to which they eventually became insensitive.

The laboratory values remained essentially normal throughout. Transient erythema was experienced by about one-fourth of the subjects immediately following some of the exposures during the first two weeks. Transient burning and stinging were reported by about three-quarters of the subjects during the first few weeks.

Investigations involving short-term, intensive exposure to 96 per cent DMSO applied twice daily to the entire trunk of twenty additional subjects were also carried out. The laboratory tests again remained normal at the end of the study. One subject was unable to complete the study because he developed a toxic reaction with diffuse erythematous, scaling rash accompanied by severe abdominal cramps. Except for cutaneous signs, the remainder of the subjects tolerated the drug. At some time during the first two weeks, most subjects complained of stinging and burning. About half displayed a transient erythema after each application. These signs and symptoms generally emerged between the second and tenth day, consistently regressing with continued application. At the end, no subject was significantly discomforted cutaneously. The erythema usually developed within fifteen to thirty minutes after the application and lasted for about twenty minutes, maximally one hour. The whealing and the transient erythema, when not accompanied by dermatitis, are readily explained as manifestations of the histamine-liberating effects of DMSO. Histamine depletion by continued administration of DMSO satisfactorily accounts for

the disappearance of these signs in a week or so.

DMSO is additionally a primary irritant in high concentration. Further studies by Kligman included intradermal injections which showed that concentrations of 50 per cent and above generally caused an inflammatory papule at 24 hours, usually not greater than 0.5 cm. in diameter, regressing within a day or two without sequelae. Conjunctival toxicity with concentrations over 50 per cent was also manifest by transient burning and mild injection but in all cases, the external eye was completely normal by 24 hours. Kligman also reported that there were no instances of allergic sensitizations occurring among the hundreds of subjects who participated in his studies, even though many of them were exposed repeatedly to concentrated doses. He also proved in his studies that irritativeness was greatly potentiated by sealed, occluded patches, which promote penetration of the irritant as well as prevent its loss.

He thus concluded that the primary irritant effect of DMSO is associated with microvesicles and epidermal death when high concentrations are applied under the unnatural condition of occlusion. The loss of selective permeability is the main cause of cell death abetted by marked hygroscopic swelling. Once or twice daily swabbing of the skin with 90 per cent DMSO will produce a mild, erythematous, scaling dermatitis in some subjects, a minority. This exposure produces mild subclinical, mainly epidermal

damage in probably all subjects. The dermatitis which is accompanied by only a moderate inflammatory reaction in the dermis, invariably regresses as treatment continues, the skin eventually becoming histologically normal. According to Kligman, none of the cutaneous effects produced by topically administered 90 per cent DMSO constitute a contraindication to the treatment of musculoskeletal and connective-tissue disorders.

E. POTENTIAL DRUG USEFULNESS OF DMSO

Nichols and Jacob[9] reported that, in clinical situations involving pain associated with inflammation, DMSO has a pronounced analgesic effect. In contrast, should DMSO be applied to a simple, non-inflamed laceration, there is minimal pain relief. With the same wound chemically inflamed or infected, pain relief is obtained. Topical application to fractures of the bones of the feet or hands permit manipulation without discomfort. Itching, a pain-like response, can be relieved in many cases. The discomfort of contact dermatitis from poison oak sensitization can be relieved in about 50 per cent of cases seen. Pain and swelling associated with a variety of acute musculoskeletal injuries are generally relieved and relief can be rapid and lasting. Ischemic ulcers, complicated by generalized scleroderma, improve following the administration of DMSO, manifested by alleviation of pain and some hastening of delayed healing.

DMSO has also been discussed by Rosenbaum[12] as a treatment of intractable pain in surgical patients. Patients suffering from tic douloureux, post amputation phantom pain, and neuralgias obtained unequivocal benefit.

Herschler and Jacob[2] reported that application of DMSO to herpes simplex generally affects rapid healing. Iodine in DMSO appears to enhance this therapeutic action with herpes simplex lesions.

DMSO applied, even topically, increases urinary output. More effective systemically administered diuretics are known but a topically applied diuretic is unique. In this area of indicated usefulness, there is clinical evidence of effectiveness as a systemic poison detoxifying agent.

Laboratory evidence reported by Herschler and Jacob[2] indicate that DMSO synergizes the depression of blood sugar with insulin and potentiates the anti-inflammatory response of cortisone and the anti-bacterial action of iodine.

DMSO has been noted to reduce the edema component, or swelling, associated with a chemical burn.[2] ~~Clinically inflammation~~ Clinically, inflammation is reduced by DMSO in a number of situations such as: infections, trauma, allergy, bursitis, acute gout, osteoarthritis, rheumatoid spondylitis, rheumatoid arthritis, fibrositis and back strains.

DMSO has also been found effective as a treatment of first, second, and third degree burns; obtaining pain relief, control of Pseudomonas infections, and improved healing.

As a topical treatment for peripheral vascular diseases, DMSO applied to patients is associated with the relief of symptoms attributed to peripheral vascular insufficiency such as intermittent claudication and ischemic ulcers.

DMSO readily crosses all the membranes of the body that have thus far been tested. Penetration is rapid and not associated with detectable injury. DMSO carries or permits passage of a number of compounds, some useful therapeutically across these barrier membranes.

It must be emphasized that confirmation of the effectiveness of DMSO in the above potential indications for use awaits further clinical experience and controlled studies. The above simply lists those conditions in which DMSO has been reported effective, though the observations may have been in only a few patients.

F. ADVERSE SIDE REACTIONS AND EFFECTS

The most common adverse reaction associated with the topical application of DMSO to the skin is some degree of burning and irritation.[8] Erythema and itching are not uncommon and occasionally

vesiculation develops. In only a small percentage of the patients treated with DMSO has the degree of skin irritation been sufficient to discontinue the application of the drug.

In addition to the localized skin irritation produced by DMSO, there has also been observed a generalized dermatitis associated with the use of this drug. It may occur after the first application of DMSO or not until DMSO has been applied for several weeks or months.

A small percentage of patients have developed paresthesias after the application of DMSO. Occasional patients have developed urticaria with wheal formation following application of DMSO. It has also been reported that extreme fatigue was noticed by a few patients using DMSO.

About half the patients have discerned, within several minutes after application, a sweet, sulphur-like, or oyster-like taste in the mouth. The air of expiration taken on a garlic-like odor. This odor is thought to be due to the excretion of dimethyl sulfide, a DMSO metabolite, through the lungs.

G. TREATMENT OF ARTHRITIS PATIENTS WITH DMSO

According to Heinz John,[5] the least satisfying results were obtained in the treatment of rheumatoid arthritis. He states that only the less severe cases responded and that they were cases with minimal systemic manifestations of rheumatism and only those cases with involvement of one or two joints responded satisfactorily.

Relatively long treatment periods were necessary in these cases to obtain satisfactory results. He did report, however, that he noted a dramatic response in his patients with gouty arthritis. He felt that cases of acute arthritis and particularly peri-arthritis and arthroses responded well to DMSO therapy.

Rosenbaum, Herschler and Jacob[10] reported the following concerning their use of DMSO in the treatment of osteoarthritis. They noted improvement in most patients with osteoarthritis involving the joints of the hand, the knee, and the ankle. Less dramatic results were achieved with DMSO in treating osteoarthritis of the hip. In this affliction, they recommend using at least 10 to 15 ml. applied to the back and buttocks twice daily and therapy continued for six to eight weeks before benefit could be expected. The frequency of application of DMSO could then be decreased as the disorder improved. In their treatment of rheumatoid arthritis, the response to DMSO was less dramatic. They found DMSO to be most effective in patients with rheumatoid arthritis who showed minimal systemic manifestations and in when the disease was limited to one or two joints. In the severe rheumatoid arthritic with marked systemic involvement, application of up to 30 ml. of DMSO per day for only two months to the involved joints was followed by minimal therapeutic benefit. On the other hand, they noted in a group of patients with grades 3 and 4 rheumatoid arthritis, six out of ten patients treated for eight to ten months were considered as

unequivocally improved. They concluded that DMSO would serve as a useful adjunct in some severe rheumatoid patients who are being treated with gold, chloroquine, phenylbutazone, or cortisone. However, they have to date noted no consistent changes in the usual anemia accompanying the disease or in the sedimentation rate. The major benefit in their opinion derived from DMSO in the rheumatoid patient is a reduction of edema and pain, thus permitting increased use of the limb. In gouty arthritis, they observed that DMSO when applied liberally to an inflamed joint and surrounding region provides relief of edema and swelling in thirty minutes lasting for from one to four hours. Repeated applications up to four times daily adequately control the pain.

II. CLINICAL INVESTIGATIONS USING DMSO

A. INPATIENTS AT DOUGLAS COUNTY HOSPITAL

In an effort to evaluate the potential usefulness of DMSO as a therapeutic agent, I have limited my clinical investigations to patients with chronic arthritic disorders including rheumatoid, gouty and osteo-arthritis. Certainly, there is a need for a good analgesic with possible anti-inflammatory properties to treat arthritic patients. Potentially at least DMSO seems to possess such capabilities. The possible usefulness of DMSO in this respect was thus primarily determined by the responses and opinions of the patients themselves who were in many cases nearly incapacitated with their pain and in all cases very anxious for pain relief.

Two different groups of patients were selected. One group consisted of six hospital inpatients at Douglas County Hospital who were selected at random and have little in common except the fact they are elderly and have been suffering from chronic arthritic conditions. These six patients were observed and questioned daily and the application of the DMSO was always performed by an attendant. Laboratory examinations, including complete blood count, urinalysis, and serum glutamic oxaloacetic transaminase determinations were performed on all patients before and after the period of therapy. Objective changes in the patients condition

were estimated by observing for changes in physical findings such as swelling, stiffness, circumference of the lesion, etc. and also by estimating, before and after treatment, the approximate range of motion of the affected joint. The patients own subjective impression was primarily used as to whether or not he experienced any significant relief of pain. The patients were instructed to report their responses to the drug in terms of pain relief as: absent, markedly decreased, moderately decreased, slightly decreased, unchanged or worse, and these were recorded as such.

All patients were treated in the same manner and for the same length of time. Treatment was confined to cutaneous administration over affected areas. The DMSO was applied to the skin with a cotton-tipped applicator, and it was swabbed over the involved area and a wide area surrounding the affected site. It was applied three times daily, morning, noon, and late afternoon, seven days a week for two straight weeks. The areas painted were allowed to become dripping wet with the solution and then dry for fifteen minutes. Usual amount applied at each time was about 4-6 ml. for a disorder involving a joint such as the shoulder or knee. In all cases, a 90 per cent concentration of DMSO in water was used. All previous therapy that the patients had been receiving for their arthritis was discontinued for this two-week period.

B. RESULTS OF TREATMENT OF DOUGLAS COUNTY HOSPITAL INPATIENTS

The results of our clinical investigations on hospital inpatients at Douglas County Hospital are presented in Tables #1 and #2. Table #1 includes personal data and the responses of the patients in terms of pain reduction and change in the mobility of the joint. Table #2 includes the most commonly reported side effects and a tabulation of the presence or absence of these side effects in each individual patient. Because of the subjective nature of most of these complaints, no attempt was made to quantitate their responses.

As recorded in Table #1, three out of the six patients reported a moderate reduction in their pain. One of these three patients, #4, noted improvement in the joints of his hands which had only recently given him trouble in acute flare-ups. This same patient reported no improvement in his chronically diseased and very painful knee. Similar results were noted in the mobility of the joints treated with three patients showing some increase in mobility and three with no change. There were no other significant objective changes noted by the observers. There also does not appear to be any correlation with the results obtained and previous therapy.

In reference to Table #2, five of the six patients reported a burning sensation with some itching and/or erythema. There also were five patients who noted the peculiar garlic-like taste or

halitosis, and one of these five became slightly nauseated. None of the six patients showed any signs of vesiculation, urticaria, or fatigue. There also were no changes in the laboratory studies performed before or after the treatment of any of the six patients.

C. OUTPATIENTS AT UNIVERSITY OF NEBRASKA HOSPITAL ARTHRITIS CLINIC

This second group of patients selected for use in determining the effectiveness of DMSO are all outpatients in the University of Nebraska Arthritis Clinic. This group offered a better variety of conditions, age, severity of disease, etc., but on the other hand, was more difficult to control since they were allowed to treat themselves at home. Each patient was simply given 30 to 60 cc. bottle of DMSO and instructed on how to apply it. He was also told of the various side effects and advised on what to expect. Most of the patients had tried several other drugs for arthritis and many were taking these drugs at the same time they were applying the DMSO. However, all were very anxious to try a new drug in hopes of relieving their pains. We have relied almost completely in this evaluation of clinical outpatients on the opinion of our patients as to its usefulness as a pain-reliever. No attempt was made at a double-blind study because of the almost universal side effect of a

detectable taste in one's mouth following application of DMSO.

D. RESULTS OF TREATMENT OF ARTHRITIS CLINIC OUTPATIENTS

Tables #3 and #4 contain the results of our clinical investigations on outpatients at the University Arthritis Clinic. In Table #3, it should be pointed out that there is considerable variance in the length of time in treatment and amount of drug used. We tried to see all patients about four weeks after the onset of therapy, but some patients did not keep their appointment on the date requested. However, all the patients were examined and questioned at one time or another. We attempted to discontinue all the patient's other therapy during our treatment with DMSO, but if DMSO was of little value, they were advised to continue their previous therapy.

As recorded in Table #3, six out of the ten patients treated reported no change in their pain; two reported slightly decreased pain and two reported moderate improvement. One patient, #3, was quite impressed the first month or so with the benefit to his wrists, but after another two weeks, he felt that it was no longer of any help. He also reported that his chronically affected knees were not helped at all by DMSO. A slight increase in mobility was noted by four of the ten patients. Objective physical changes were not significantly improved.

Table #4 is a report of the side effects experienced by this

group of patients. Once again, we note the low order of toxicity with only transient minor effects reported. All ten patients reported transient burning sensations usually accompanied by some itching or erythema. One patient reported vesiculation and discontinued using the drug because of it, even though it was painless and not particularly bothersome to her. Nine of the ten patients reported the characteristic odor on their breath. There were no other complaints.

At the end of each individual time of treatment, none of the ten patients cared much either way if they continued their therapy with DMSO. Most of them were of the opinion that it was neither as good as or certainly no better than their previous therapy. However, none of them cared to stop their treatment because of side effects.

III. TABLES

TABLE #1

RESULTS OF TREATMENT WITH DMSO OF ARTHRITIS PATIENTS AT DOUGLAS COUNTY HOSPITAL

T	AGE	DIAGNOSIS*	DURATION	PREVIOUS THERAPY	AREAS TREATED	AMOUNT	DOSAGE AND ADMINISTRATION	PAIN**	MOBILITY***
M.	65	R.A.	15 years	Salicylates	both hands left knee	90% (60cc.)	t.i.d. 2 weeks	++	+
F.	72	R.A.	10 years	Salicylates Gold	left elbow both hands	90% (60cc.)	t.i.d. 2 weeks	o	o
G.	70	R.A.	16 years	Salicylates Cortico-steroids	left knee left hand left shoulder	90% (60cc.)	t.i.d. 2 weeks	o	o
.	74	R.A.	10 years	Butazolidin Cortico-steroids	right hand right knee	90% (60cc.)	t.i.d. 2 weeks	++	++
.	81	R.A.	10 years	Salicylates Gold	right knee	90% (60cc.)	t.i.d. 2 weeks	o	o
.	82	O.A.	15 years	Salicylates	right hip	90% (60cc.)	t.i.d. 2 weeks	++	+

- gouty arthritis, R.A. - rheumatoid arthritis, O.A. - osteo-arthritis
- absent, +++ - markedly decreased, ++ - moderately decreased, + - slightly decreased, o - unchanged, - worse
- markedly increased, ++ - moderately increased, + - slightly increased, o - unchanged, - worse

TABLE #2

SIDE EFFECTS REPORTED BY ARTHRITIS PATIENTS TREATED WITH DMSO AT DOUGLAS COUNTY HOSPITAL

PATIENT	HALITOSIS	BURNING OR IRRITATION	ITCHING	ERYTHEMA	VESICULATION	URTICARIA	FATIGUE
(1) Mrs. A.M.	yes	yes	yes	none	none	none	none
(2) Mrs. E.F.	none	yes	yes	yes	none	none	none
(3) Mrs. B.G.	yes	yes	yes	none	none	none	none
(4) Mr. M.V.	yes	yes	none	none	none	none	none
(5) Mr. O.G.	yes	yes	yes	yes	none	none	none
(6) Mr. A.G.	yes	none	none	none	none	none	none

TABLE #3

RESULTS OF TREATMENT WITH DMSO OF ARTHRITIS PATIENTS AT UNIVERSITY ARTHRITIS CLINIC

T	AGE	DIAGNOSIS*	DURATION	PREVIOUS THERAPY	AREAS TREATED	AMOUNT	DOSAGE AND ADMINISTRATION	PAIN**	MOBILITY***
.	62	G.A.	10 years	Colchicine Zacterin	left knee	90% (30cc.)	t.i.d. 1 month	+	o
.	57	R.A.	6-7 years	Salicylates	both hands	90% (60cc.)	t.i.d. 5 weeks	o	o
M.	49	R.A.	7-8 years	Salicylates Gold Cortico-steroids	both knees and wrists	90% (90cc.)	t.i.d. 2 months	++	+
.	62	R.A.	21 years	Salicylates Cortico-steroids	left ankle and knee	90% (30cc.)	t.i.d. 1 month	o	o
L.	70	R.A.	20 years	Darvon	right hand	90% (30cc.)	t.i.d. 1 month	o	o

TABLE #3 cont'd.

RESULTS OF TREATMENT WITH DMSO OF ARTHRITIS PATIENTS AT UNIVERSITY ARTHRITIS CLINIC

T	AGE	DIAGNOSIS*	DURATION	PREVIOUS THERAPY	AREAS TREATED	AMOUNT	DOSAGE AND ADMINISTRATION	PAIN**	MOBILITY***
P.	72	R.S.	31 years	Darvon Cortico-steroids	right hand	90% (30cc.)	t.i.d. 1 month	o	+
T.	71	G.A.	17 years	Probenecid	both knees	90% (60cc.)	t.i.d. 6 weeks	+	+
.	69	R.A.	3-5years	Darvon	both hands	90% (30cc.)	t.i.d. 1 month	++	+
H.	42	R.A.	16 years	Salicylates Cortico-steroids	both hands and feet	90% (50cc.)	t.i.d. 1 month	o	o
.	58	R.A.	5-7 years	Salicylates	right shoulder	90% (30cc.)	t.i.d. 1 month	o	o

TABLE #4

SIDE EFFECTS REPORTED BY ARTHRITIS PATIENTS TREATED WITH DMSO AT UNIVERSITY ARTHRITIS CLINIC

PATIENT	HALITOSIS	BURNING OR IRRITATION	ITCHING	ERYTHEMA	VESICULATION	URTICARIA	FATIGUE
(1) Mr. E.M.	yes	yes	yes	yes	none	none	none
(2) Mr. R.D.	yes	yes	yes	yes	none	none	none
(3) Mrs. L.M.	none	yes	yes	none	none	none	none
(4) Mr. O.H.	yes	yes	yes	none	none	none	none
(5) Mrs. E.L.	yes	yes	yes	none	none	none	none
(6) Mrs. E.P.	yes	yes	none	none	none	none	none
(7) Mrs. O.T.	yes	yes	none	none	none	none	none
(8) Mr. R.K.	yes	yes	yes	yes	yes	none	none
(9) Mrs. H.H.	yes	yes	none	none	none	none	none
(10) Mr. R.H.	yes	yes	none	none	none	none	none

IV. CONCLUSIONS

The purpose of this thesis has been to review briefly the literature relevant to dimethyl sulfoxide and to present the results of my clinical investigations. DMSO has been used on sixteen patients with chronic arthritic disorders in an attempt to evaluate its usefulness as a therapeutic agent and its possible adverse effects. Patients suffering from chronic arthritic disorders are certainly in need of a new drug for relief of pain, and all of the patients were willing and eager to participate in this study. For the sake of simplicity and unity, this study was limited to chronic arthritic disorders.

The few reports in the literature concerning the use of DMSO in arthritic disorders have been rather discouraging as to its effectiveness. In general, they were of the opinion that only the less severe cases and those with minimal systemic manifestations and involvement of only one or two joints responded at all. The main benefit of DMSO, they felt, was probably the reduction of edema and pain which permits increased use of a limb.

My clinical investigations included six inpatients at Douglas County Hospital and ten outpatients from the Arthritis Clinic at University of Nebraska Hospital. The first group was carefully controlled and observed daily for subjective and objective changes. The second group of outpatients were instructed on

proper administration of DMSO and possible side effects and thoroughly questioned on their return visits to the Clinic.

Judging from the responses of these patients under investigation, it is my opinion that DMSO offers little promise as a therapeutic agent in the treatment of chronic arthritic disorders. DMSO could conceivably be of some benefit in acute flare-ups or less chronic types of arthritis but probably not of any greater value than the conventional analgesics such as salicylates in chronic arthritics. The subjective response of each patient as to whether or not he received any significant pain-relief and his own opinion of the drug ~~was~~ were primarily used as a guide to the effectiveness of DMSO. In not one case did the patient feel that DMSO was better or even as good as his previous medication. Despite a few encouraging responses, there was no overwhelming enthusiasm for the drug and no one who requested further use of DMSO after the trial dosage.

On the other hand, no one asked to discontinue the drug because of adverse side effects. The toxicity that was manifested was only transient.

Irregardless of the rather discouraging findings in arthritic patients, I am still intrigued by the reported possibilities of DMSO in treatment of other disorders. I am regretful that at this time further clinical investigations on human subjects are impossible. However, I am hopeful that these investigations will be resumed sometime in the future.

V. SUMMARY

This thesis has been concerned with a resume of the current literature pertaining to the history, chemistry, pharmacology, toxicity, usefulness and side effects of dimethyl sulfoxide and primarily a clinical investigation using DMSO on chronic arthritic patients. Six patients have been treated and closely observed at the Douglas County Hospital, and ten patients have been treated from the University of Nebraska Arthritis Clinic. The results of these studies are recorded in the Tables.

The conclusion of this study is that DMSO is probably not of any value in the treatment of chronic arthritic disorders but that its adverse side effects are minimal and not a contra-indication to its use.

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