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Biological Actions and Medical Applications of Dimethyl Sulfoxide

DMSO

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BIOLOGICAL ACTIONS AND MEDICAL APPLICATIONS OF DIMETHYL SULFOXIDE

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BIOLOGICAL ACTIONS AND MEDICAL APPLICATIONS OF DIMETHYL SULFOXIDE

DIMETHYL SULFOXIDE: THE GOLDEN MAZE DILEMMA

The English poet and dramatist John Dryden once wrote: "I think and think of things impossible, yet love to wander in that golden maze."

Dimethyl sulfoxide (DMSO) is a compound that has been in a type of "golden maze" for some time. Twenty years have passed since DMSO was reported to have a number of unusual biological activities. During this period of time, there has been a steady outpouring of scientific papers as well as half a dozen international conferences that have examined the biochemical and pharmacological properties of DMSO on multiplex organic systems. Less work has been done on the clinical applications of DMSO for use in patients despite its apparent relative safety and its potential ability to reverse some life-threatening crises. For example, it's powerful diuretic effect, reported to be greater than furosemide, could be of immediate clinical relevance either as an adjuvant or primary therapy in such potentially fatal conditions as congestive heart failure, pulmonary edema, nephrotic syndrome, cerebral edema, acute renal failure, hepatic cirrhosis, and others. A number of papers in this volume do in fact present other new and exciting applications for DMSO using well-designed experimental protocols.

One of the arguments in the past has been that only double-blind studies can provide proof of drug efficacy by eliminating experimental bias. While this may be true for some drugs in certain clinical disorders, it is not compelling in many cases where DMSO is used since there are now a number of sophisticated bedside and laboratory tests that readily provide measurable end-point values that can be quantitated for statistical analyses or cause and effect relationships.

As researchers, we rely on scientific objectivity to test the validity of a hypothesis, such as whether a drug is effective on a disease process. For example, if research studies consistently show that tissue ischemia is reversed after using drug X, it seems safe to advance the notion that such a drug has potential in modifying ischemic disorders. If in addition, drug X is also shown to reduce subjective painful sensation in humans after its administration, and this phenomenon is supported by animal data under more rigidly controlled conditions, it is again not unreasonable to conclude that drug X could be useful in reducing pain as well. If drug X also happens to be relatively safe, that is, relative to similar drugs on the market, it would be well-advised for all concerned to plan and quickly initiate clinical trials, since pain or ischemia are highly undesirable.

This is the present status of DMSO, even when only two examples of its biological activities are cited among the many presented at this symposium and elsewhere. Dr. Arthur Scherbel, in his summary statement of the 1975 and the present conference, reviewed some of the factors that have stalled clinical testing of DMSO in this country. He recommended a halt to rhetoric and the implementation of carefully designed, rigidly controlled clinical trials to evaluate the efficacy of DMSO in selected disorders.

It is hoped that the new Food and Drug Administration officials will also review these scientific studies and others now in progress, from a perspective that will effectively reduce unnecessary delays in all phases of testing. The advantages of such action, would still uphold the rigorous scientific requirements that guide Food and Drug Administration decisions in approving a drug for the consumer market, but it would also emphasize a humanistic concern for those with pain and illness that in my judgement is a truer reflection of the degree of our civilized behavior.

J. C. de la Torre

INTRODUCTORY REMARKS: DIMETHYL SULFOXIDE AFTER TWENTY YEARS

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We have entered the third decade of research on DMSO as a biological agent. Unfortunately, medical science is still confronting political barriers blocking availability of DMSO as a safe and effective prescription drug. Fortunately the non-medical biological uses for DMSO steadily unfold, demonstrating an amazing diversity of applications.

Should we be satisfied with this status? Perhaps our humanitarian instincts must be sequestered. Whatever the regulatory position in the United States through the 1980s and beyond, mankind has forever lost the optimum economic benefits of a substance with a drum-lot price that could and should not be over a half dollar a pound. At present, a 50% aqueous solution, 50-ml size, for bladder instillation retails in the range of $13.00 while an eight-ounce bottle of nearly anhydrous DMSO for platelet preservation is priced in the range of $100.00.

As one reviews the literature of the past several years, it is apparent that while severe regulatory constraints have suffocated clinical developments with DMSO, other scientific studies, not subject to regulatory overkill, are flourishing to man's benefit.

A status review of the diversity of scientific studies is beyond the scope of this discussion. Only a few areas of special interest have been selected for brief mention here.

The profound effects of DMSO on the growth and morphology of human and lower animal tumor cells have challenged the investigative talents of workers throughout the world. These studies provide a clearer understanding of the processes of malignancy and may lead to better therapy.

Neutralization of trauma-induced pathology to the brain and spinal cord is dramatic and exciting.

Immunological implications from various studies concerned with cell-mediated immunity, competition for receptor sites, or modified pheresic applications that reduce the body titer of disease-inducing immunoglobins via the renal pathway, capitalize on the basic pharmacology and chemistry of DMSO.

Studies defining mutagens and carcinogens utilize DMSO as the safe solvent and carrier. The ability of DMSO to move freely in the humoral fluid and to cross membranes without irreversible damage first attracted our attention. Because various membranes do not act as barriers to DMSO, exciting new findings have been described, as with biological free radicals.

Thus far, studies with DMSO in combination with antineoplastic agents, autoimmune potentiating agents, radiation, or hyperthermic therapy have not progressed as we projected 20 years ago. Philosophically one may speculate as to where the fault lies. Is it possible that the current regulatory fad against combination drug therapy is hindering research? Everyone recognizes that treating one disease with a single therapeutic method is both neat and precise. It is likely, however, that cancer requires a multivalent attack since it is hardly a single neat and precise disease.

Cryobiology as a discipline could hardly exist without DMSO. Biological safety, tissue and cytoplasm mobility, together with an exceptional association with water, which alters freezing properties, are characteristics of DMSO that contribute to the successful preservation of biologicals from subcellular units to the intact embryo.

The cell, the basic unit of eukaryotic life, depends on many structures. The literature teaches that DMSO can strongly influence the development of cellular structures. The effect of actin- and tubulin-production stimulation by DMSO, as demonstrated by several investigations, is at present unclear. It does seem that such findings may lead to modes of therapy with DMSO where cell normalcy is restored after disease alteration.

We now know that mitochondria and other components of cells are protected against lethal challenges, such as hypoxia, by DMSO. It is important to recognize that once DMSO enters a biologic system it becomes a ubiquitous molecule able to scavenge intracellular [OH^-] free radicals, a primary trigger of the inflammation process. One must be impressed with the ability of DMSO to not only protect but repair cells damaged by hyperosmotic challenge. Recent studies associated with the use of DMSO with brain trauma demonstrate that the body can tolerate elevated hyperosmotic pressure, perhaps a doubling of normal. This acceptable stress, like radiation, hyperthermia, and chemotherapy (possibly together with these entities), should be studied with malignancy, infections, and other disease categories.

Detoxification by DMSO of diverse chemical toxicants that induce cytotoxicity or mutagenicity were not predictable in the early 1960s. Yet one of the earliest findings with DMSO demonstrated protection against potentially lethal radiation. We have been particularly impressed with the demonstration that DMSO protects the glial cells from damage by otherwise lethal ultrasonic waves. Since each system we consider is a stress system (generally antagonistic to life) and DMSO is a protectant of life under such stress, therefore is not protection against stress a unique, new pharmacologic parameter of usefulness to DMSO's credit? Why isn't this pharmacologic parameter used more generally to improve the practice of medicine?

The physical barrier (generally termed blood-brain barrier) limiting movement into the brain makes it difficult to carry out effective drug therapy. While DMSO moves freely across this barrier, early results as a vehicle/carrier were disappointing. Newer techniques demonstrate improved carrier action. Predictably in the next decade, refinements will be described that could benefit the health and welfare of mankind.

One can hardly await the findings of the next ten years concerning the role of DMSO and metabolites, particularly methylsulfonylmethane, as preferred substrates attracted to receptor sites. Seemingly, DMSO has a role to play in the field of immunology. What factor or technique is yet to be discovered that will complete the building of a medically useful system?

Workers in Europe and Asia have further contributed to our knowledge of the potential of DMSO with infective diseases. Basic and clinical findings teach the usefulness of combinations. Both DMSO and antibiotics are membrane active. In our view a yet unrecognized factor limits optimizing the medical usefulness of such combinations. Great benefits can be reaped if we learn how to better use the extensive list of developed antibiotics rather than continuing to spend irreplaceable resources developing new products to overcome antibiotic resistance.

Having reflected on the past 20 years, a few predictions seem appropriate concerning the future of DMSO in the biological sciences.

It is unlikely that the Food and Drug Administration (FDA) will continue to be successful in blocking DMSO in medicine. Nevertheless, irrespective of the field of research and not limited to DMSO, scientists everywhere face an ever increasing threat of confrontation directly or indirectly with the FDA. Regrettably one cannot exclude the likelihood that with this ever increasing conflict the health of the patient will be compromised.

It seems a certainty that for economic, humanitarian, and scientific reasons, state governments will increasingly intervene in the case of DMSO to protect and improve the health and welfare of the citizenry, and for the legal protection of physicians.

If the Congress of the United States passes legislation excluding the FDA from all regulatory concern with DMSO, we hope that one major reason is the desire of Congress to establish a testing of the efficacy of today's law, which appears to have been written and implemented by the FDA to satisfy a vocal but radical minority. It would be reasonable, two decades after enacting (with some haste) the 1962 drug law revisions, to ascertain whether the present food and drug laws, as implemented by the FDA, are a service or disservice to our people. Both the Congress and the executive branch of our government must feel concern for the millions who now are unable to seek benefit from new drug therapies solely for economic reasons. These reasons are traceable to the cost of the new drug approval process. It now costs more to secure a drug approval then it did to wage war in the last century. If DMSO is made exempt from FDA control, the price of medical DMSO will drop sharply from about $10.00/ounce (DMSO content basis) to roughly forty cents per ounce—allowing in this price for special implementation and research support taxes. Beyond the obvious benefit to the consumer of the approximate $9.60/ounce drop in price, superior formulas with lessened side effects can be provided. Two such formulas now used at the DMSO clinic at the Oregon Health Sciences University are suggested product candidates with intrastate regulated DMSO. Each is an excellent topical product with demonstrated safety and efficacy.

Urea-modified DMSO moderates nuisance-type side effects. The sulfurish breath, skin irritation, and occasional itching as well as skin dryness are lessened. A typical formulation (by weight) is: 60 parts DMSO, 20 parts urea, and 20 parts water. This formulation can be gelled or administered as a liquid for disorders of the musculoskeletal system.

The addition of the potassium salt of para-aminobenzoic acid (KPABA) provides a useful topical agent with various collagen disorders such as scleroderma, Peyronie's disease, Dupuytren's contracture, and hypertrophic scar. One useful formula (by weight) is: 70 parts DMSO, 15 parts urea, 7.5 parts water, and 7.5 parts KPABA.

One product of DMSO appears to have a bright scientific and commercial future. This is the stable metabolite of DMSO referred to as methylsulfonylmethane or MSM. We now refer to it as Factor N, with the intended implication that this biochemical helps maintain our bodies within normal or good health parameters. We predict this will receive international attention as a dietary supplement, interestingly found in particularly high concentration in what has been referred to as the nearly perfect food. The precursors of Factor N, the various salts of dimethyl sulfide, and even DMSO, are found in most of the foods that vertebrates use. Precursor conversion to MSM is accomplished enzymatically. Unfortunately unless our diet is almost solely milk, it appears that our bodies have a possible deficiency.

MSM, an odorless, essentially tasteless, white crystalline chemical demon-

strates usefulness as a dietary supplement in man and lower animals. Our research suggests that a minimum concentration in the body may be critical to both normal function and structure.

Limited studies suggest that the systemic concentration of MSM drops in mammals with increasing age. This may be due to dietary habits where one ingests foods with lower MSM potential with maturity or possibly there is a change in the renal threshold. Healthy juvenile rabbits maintain a level at or above 1 ppm body weight, with milk being the dominant food and source. Cow's milk normally contains between 2 and 6 ppm MSM dependent on source and freshness. In an adult man, the circulating concentration varies but may average about 0.2–0.25 ppm. We have no estimate of total body concentration as yet but suspect that MSM is banked in some of the organs, other than the adrenals. Based on radiolabel (^{35}S) studies, the residence time of a single challenge in mammals may be several weeks with gradual dumping via the renal system. Daily output of urine contains several milligrams of MSM. This possibly is not the dominant excretory route.

The following abnormal conditions seen in the clinic have responded to oral MSM generally administered at dosage levels of 250–750 mg/day.

(1) Response to allergy. Oral MSM moderates diverse allergic responses as to pollen and foods. Antiallergy medication and desensitization methods may be sharply reduced.

(2) Control of hyperacidity. Subjects seen to be chronic users of various antacids and histamine H_2 receptor antagonists prefer MSM by reason of relief obtained coupled with freedom from serious, untoward effects.

(3) Hypersensitivity to drugs. Subjects demonstrating drug hypersensitivity as to aspirin, several nonsteroid antiarthritic agents (Naprosyn, Indocin, Motrin), and oral antibiotics, were drug tolerant when MSM was given within an hour before or concurrent with the sensitizing drug.

(4) Control of constipation. Particularly in the older population seen in our clinic, chronic constipation can be a medical problem of concern. To date, over 50 subjects presenting chronic constipation have gained prompt and continuing relief by supplementing the diet with 100 to 500 mg of MSM per day.

(5) We have seen some individuals with severely restricted lung function. Of these, only a few cooperated in vital function assessments. All cooperated in endurance measurements, however. Limited objective and strong subjective evidence suggests the MSM is a useful dietary supplement to reduce lung dysfunction.

(6) Antiparasitic action. *In vitro* and *in vivo* tests suggest MSM has activity against a variety of medically important parasitic problems. Thus far work has concentrated on parasitic problems of the intestinal and urogenital tracts. MSM, for example, is active against Giardia, Trichomonads, and round worms. MSM may effect such infections by competing for binding or receptor sites at the mucous membrane surface presenting a blocking interface between host and parasite. We are at present evaluating the action of MSM with a variety of abnormal or medical problems to determine whether any are responsive to a diet supplemented by MSM. One facinating aspect of this work is the observation that with presented function and structure normalcy, MSM appears to be inactive pharmacologically. Only where abnormality occurs have we seen MSM influence a return towards normalcy, defined as being within measurable parameters of good health.

We are intrigued by the fact that MSM is a constant factor in all normal diets of vertebrates and somewhat mystified by the seeming need of the body of adults

for a concentration level above that available from a diet presumed as "normal." We hope soon to have data defining any specific interacting role that MSM may have with the water-soluble vitamins, particularly vitamin C, which like MSM is reportedly banked in the adrenals.

It is not possible to directly compare DMSO and derivative MSM, though of the same chemical family. Each is unique unto itself. MSM is a dietary factor derivable from most natural foods. It is conveniently taken alone, or in foods. Taken by mouth, there is no afterbreath. DMSO has certain unpleasant attributes not possessed by MSM.

While MSM is a dietary factor, DMSO is not. DMSO readily penetrates the dermis and less complicated membrane systems while MSM does not. Each contributes to the well-being of mankind, but in differing ways. Both have important implications.

When Dr. Chauncey Leake summarized the first New York Academy of Sciences Symposium on DMSO he said that the well-known legal phrase of *res ipsa loquitur* applied to the DMSO controversy, stating that "rarely had a new drug came to the attention of the scientific community with so much verifiable information from so many parts of the world." Those remarks were true in 1965. They remain true today.

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Editor and Conference Chairman
J. C. DE LA TORRE

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THE STATUS OF DIMETHYL SULFOXIDE FROM THE PERSPECTIVE OF THE FOOD AND DRUG ADMINISTRATION

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I'm pleased to represent the Food and Drug Administration (FDA) in this volume. I will review the history of DMSO as recorded at the FDA, comment on its current status, and finally, from my prospective as a reviewer, offer some of my own observations and comments.

Since 1963, when Dr. Stanley W. Jacob reported that DMSO penetrates skin rapidly, aids the transport of other drugs across biological membranes, has local analgesic activity, and decreases swelling and promotes healing of injured tissue; DMSO has attracted continuing pubic attention as a potential therapeutic agent in a variety of diseases.

The first investigational new drug exemption (IND) for the study of DMSO in humans was filed with the FDA in 1963. Enormous interest in the drug developed rapidly and it began to be used widely, especially for the treatment of sprains, bruises, and minor burns. By late 1965, an estimated 100,000 patients had received the drug. However, no well-controlled studies were conducted to document clearly that the observed effects were actually caused by the drug. This widespread, uncontrolled use of DMSO was curtailed sharply in November 1965, when the FDA terminated all clinical studies of DMSO because of toxicological studies showing that the drug changed the refractive index of the lens of the eye in experimental animals. The agency's concern at the time was that visual damage might occur in humans exposed to the drug.

A year later this policy was relaxed to permit clinical evaluation of DMSO "... in serious conditions, such as scleroderma, persistent *herpes zoster*, and severe rheumatoid arthritis, for which no satisfactory therapy is now available."

In September 1968, the FDA published a further revision of its DMSO policy permitting topical application to the skin for no more than 14 days for treatment of less serious disabilities, such as acute musculoskeletal conditions (e.g., sprains, bursitis, and tendonitis). This was based on a toxicological study in humans that provided a reassuring result; that is, no evidence of eye toxicity associated with the short-term application of large doses to human volunteers.

In light of the continued lack of evidence of eye damage in humans since that time, the FDA concluded that the regulation establishing specific requirements for clinical testing of DMSO in humans was no longer necessary, so it was revoked in May 1980. Since that time the regulations governing DMSO have been essentially the same as those regulating other investigational drug substances. However, in response to attempts by distributors to sell "not for medical use" DMSO to obvious medical users, the FDA has monitored DMSO distribution and shipments somewhat more closely than other IND drugs.

Similarly, some INDs submitted by individual investigators have been thinly

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veiled attempts to get "legal" DMSO to use, not to study. FDA has insisted that DMSO studies under INDs be well-controlled and we have spent considerable time helping less experienced but well-motivated investigators and sponsors design trials that would be adequate to serve as a basis for new drug approval. We will return to what the FDA considers appropriate clinical study design later.

Because of continuing controversy over the FDA's position on DMSO, Dr. Charles C. Edwards, then Commissioner of the FDA, asked the National Academy of Sciences in 1972 to review all available information on the safety and effectiveness of DMSO and provide the FDA and the Congress with an independent judgement on these matters. The National Academy of Sciences appointed a distinguished primary committee with six subcommittees to conduct this review. They screened and reviewed the literature consisting of some 1,200 papers on DMSO, including the proceedings of the first New York Academy of Sciences Symposium on DMSO held in 1966.* In addition they reviewed 193 volumes of reports submitted to the FDA. To this day, the National Academy of Sciences' review stands as the most comprehensive independent evaluation of DMSO by the medical and scientific community.

The Academy concluded that there was inadequate scientific evidence of effectiveness of DMSO for the treatment of any disease; that the toxicity potential of DMSO was sufficiently great that the drug should remain investigational; and that controlled clinical trials were necessary to demonstrate the effectiveness of DMSO. A further conclusion of the Subcommittee on Connective Tissue Diseases was "... that most of the studies reviewed were of such poor quality as to be useless for its purposes...." We will return to this last conclusion when we consider what constitutes appropriate clinical trials.

Prior to 1972, there were 69 INDs filed for DMSO uses ranging from cryopreservation of cells and treatment of frostbite, to treatment of *herpes zoster* and phantom limb pain. However, the majority of the INDs were for use of the drug in inflammatory conditions, including acute trauma, and chronic conditions, like arthritis and scleroderma. Seventy additional INDs were filed from 1972 through the end of August 1982. These for the most part have been for the same indications with the addition of studies of the effect of DMSO on mental retardation, amyloidosis, retinitis pigmentosa, spinal cord injury, cerebral edema, and bone pain secondary to malignancies. There have been studies of the use of DMSO to enhance transdermal absorption of other drugs but so far no product has emerged from these studies. Currently there are about 35 active INDs for studying DMSO.

Prior to 1972, there were three New Drug Applications (NDAs) submitted for anti-inflammatory indications for DMSO. None were approvable. Since 1972, there have been two additional NDA submissions. One was approved for intravesicular use of 50% DMSO for interstitial cystitis. The other NDA for use of DMSO in the treatment of scleroderma was judged to be non-approvable after re-review at three levels within the FDA. This latter usage is currently being studied under a National Institutes of Health contract for the Cooperative Systematic Studies of Rheumatic Diseases. The study is expected to be completed in six months.

Irregularities were discovered during an audit of the data of one of the interstitial cystitis investigators. Further investigation led to the disqualification of one clinical investigator and part way through the disqualification procedure two other investigators agreed not to do any further clinical studies under INDs. This

*Ann. N.Y. Acad. Sci. 1967. Volume 141.