THE PHARMACOLOGY OF DIMETHYL SULFOXIDE 6544

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INTRODUCTION

Synthesis and manufacture.—Dimethyl sulfoxide (DMSO) was first prepared by the oxidation of dimethyl sulfide by Alexander Saytzeff (1) in 1867. The title of his paper, "On the Influence of Nitric Acid on Methyl Sulfide and Ethyl Sulfide," deserves a moment's reflection. DMSO remained a chemical curiosity until the 1940s when the plastic industry noted its unique solvent properties (2, 3). Further research and development introduced DMSO as a solvent for insecticides, fungicides, and herbicides, and in a number of industrial processes.

Commercial DMSO was produced by the Stepan Chemical Company, Chicago, from the late 1940s until 1959 when an explosion in their plant terminated this endeavor (2). In 1956 Crown Zellerbach Corporation, Camas, Washington, became interested in the commercial possibilities of using the lignin in the kraft pulping liquor wastes and built a plant to produce dimethyl sulfide for research and developmental purposes. By 1960 the industrial use of DMSO encouraged Crown Zellerbach to build "a fully integrated dimethyl sulfide-dimethyl sulfoxide operation" at Bogalusa, Louisiana (3). More than five million pounds of DMSO were produced in 1964 (2) and the cost of the commercial product, when shipped in drums and carload lots was about 35 cents per pound (4).

Lignin (5), the source of DMSO, is a polymer of unknown chemical structure but similar to coniferyl alcohol since, like the latter, it can be oxidized to vanillin and hydrogenated to cyclohexylpropyl type compounds. Wood contains about 25–30% lignin and sulfite waste liquors up to 6%. In 1962 Crown Zellerbach obtained a patent for the processing of this "black liquor" waste, which utilized the methyl groups of kraft lignin by adding molten sulfur to form dimethyl sulfide (6, 7). Nitrogen tetroxide was then used to oxidize the dimethyl sulfide to dimethyl sulfoxide.

Discovery of biological action.—In seeking a relatively pure solution of DMSO for use as a cryostatic agent to protect organ transplants against freezing damage while in storage Dr. Stanley Jacob (6) contacted Mr. Robert Herschler of Crown Zellerbach, who related to Jacob some of the peculiar chemical and "therapeutic" properties of DMSO such as: (*a*) its ability

to extract and "wash out" 90% phenol spilled on the skin thus preventing the usual phenol eschar[1] (*b*) rapid penetrability through synthetic rubber gloves and, on one occasion, carrying enough organophosphorous insecticide through the gloves and skin to cause mild systemic poisoning (6, 8); (*c*) a stronger and more persistent dyeing of the skin of workers from accidental spilling of basic dyes in DMSO than that noted from water or alcoholic solutions of these dyes. Jacob & Herschler then demonstrated relief of pain and swelling when 100% DMSO was daubed on the skin to treat a sprained ankle or "an acute arthritic left thumb", and rapid appearance of garlic-like odor on breath, and taste in mouth, when DMSO was spilled on or applied to skin.

A number of experiments were then started at the University of Oregon Medical School to obtain evidence that DMSO was an active penetrant and carrier of other substances through the skin or tissue membranes. The initial report (9) demonstrated that DMSO enhanced the absorption of heparin, insulin, sodium salicylate, Evans Blue dye, sulfadiazine, aminophylline, and thio TEPA through the intact urinary bladder of the dog.

In earlier biological studies, Lovelock & Bishop (10) had demonstrated in 1959 that DMSO was more effective than glycerol in protecting bull spermatozoa from freeze-thaw damage. Then in 1962 Ashwood-Smith (11) reported on DMSO "as a cryoprotective agent in a large number of mammalian and nonmammalian cells and tissues" (12). He also studied the protective action of DMSO against X-irradiation, and speculated (13) that DMSO might prove of value as a relatively innocuous solvent for intravenous and intraperitoneal administration of some water-insoluble agents.

Chemistry

Chemical characteristics.—DMSO is classified chemically as a dipolar, aprotic hydroscopic solvent (14, 15). Protic solvents such as water, methanol, and formamide are hydrogen donors. Dipolar aprotic solvents, although possessing hydrogen atoms, lack the ability to donate labile hydrogen atoms to form strong hydrogen bonds with certain other substances. Other dipolar aprotic solvents are dimethylformamide (DMF), dimethylacetamide (DMAC), acetone, nitromethane, acetonitrile, nitrobenzene, and sulfur dioxide (16).

Structurally, the DMSO molecule appears pyramidal in shape (17) or like a tetrahedron (16) with the sulfur atom in the center and the two methyl groups, the oxygen atom, and a nonbonding electron pair located at the apices. The polarity of the sulfur-oxygen bond, with both atoms separated by an appreciable distance and located at opposite terminals, is shown in Rammler's (18) diagram (Figure 1). The marked polarity of the S-O bond is responsible for the high dielectric constant (above 45) of DMSO in liquid form. Likewise, as the result of dipole-dipole attractions of the S-O dipole the molecules of DMSO are held together in the liquid state in a chainlike order (19). In this respect some of the solvent characteristics of

[1] R. J. Herschler, Personal Communication, April 1963.

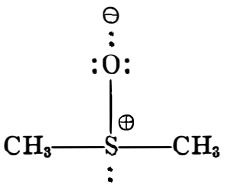

FIGURE 1. Polarized form of DMSO.

DMSO may be due to the formation of relatively stable nonperturbant solvates by molecular dipole-dipole interactions. Or, these solvent-solute associations may result from hydrophic transactions.

The aprotic nature of DMSO is indicated by its inability, usually, to donate its own protons in chemical interactions. On the other hand, sometimes the DMSO molecule will pick up protons from other molecules. The dipolar nucleophilic characteristics of the molecule are due to the availability of free electron pairs at the oxygen or sulfur terminals. This contributes to the versatility of DMSO both as a solvent and as a reagent since these electrons may be shared or transferred to other protons (16). In most cases aprotic solvents like DMSO in various liquid media act neither as an acid nor a base.

DMSO is completely miscible with water; this takes place with some evolution of heat. The considerable hydroscopic ability of DMSO may explain some of the changes in biologic activities induced by this solvent. Based on Cowie & Toporowski's (20) report, Rammler (21) suggests that a 2:1 association complex is formed between water and DMSO (Figure 2). In the hydrate form the attraction of the hydrogen bonds between water and DMSO is greater than that existing between the water molecules. In this respect MacGregor (15) notes that DMSO acts as an acceptor "atom" in hydrogen bonding and that between DMSO and water this activity is 1⅓ times as strong as between water-water. The increased hydrogen bonding activity of DMSO with water molecules and the greater activity of its anionic oxygen atom differentiate DMSO from other aprotic solvents.

DMSO is a better solvent than water for many substances, including some of relatively high molecular weight, that contain hydroxyl or other hydrogen bond donor groups. Szmant (16) lists 17 "hydrogen bond donor" substances of this type including glycerine, Nylon-6, stearic acid, sucrose, urea, and viscose rayon. Simple amino acids, however, are less soluble in DMSO than water as "water is a hydrogen bond donor as well as an acceptor . . . while DMSO is limited to the latter role."

Polarizable nonionic proteins and steroids are often soluble in DMSO. The ability of DMSO to penetrate skin and mucous membranes may be the result of its dynamic interaction with tissue water. In the living cell "nonsoluble" highly organized proteins, nucleic acids, and polysaccharides are bonded together and covered by an "icelike" sheath of water (16). In this hydration sheath the water molecules act as hydrogen bond acceptors or

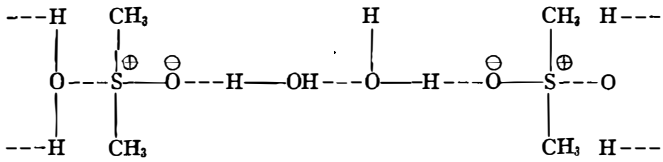

FIGURE 2. Possible structural form for hydrated DMSO.

donors, arrange themselves as highly ordered aggregates, and through the formation of "hydrophobic bonds" attach to proteins. These interactions and forces determine the native structure of the particular protein concerned. When DMSO comes into contact with these cells or membranes, it replaces the water molecule as a hydrogen bond acceptor and associates with certain "exposed" moieties (such as N-H and O-H) in the protein structure. Szmant (16) points out that while DMSO cannot compare with water as a hydrogen bond donor, it is "superior to water in associations based on the induction of dipoles in aromatic rings, methylmercapto and disulfide bonds, and so forth." The alteration in the configuration of immobile protein structures brought about by DMSO exchanging sites with bound water molecules may explain the penetration of DMSO through the skin. The transfer of DMSO across the dermal barrier is accomplished rapidly and completely without irreversible tissue damage and the alterations in protein structure are reversible. In addition, the carrier action may be due to the formation of loose and flexible areas in the epidermis by DMSO replacement of some of the bound water in the protein.

ABSORPTION

Membrane penetrability.—The rapidity, ease, and completeness of absorption of DMSO through the intact dermis and other membranes without causing irreversible damage sets apart this unique solvent from others.

Animal studies.—McDermot, Murray & Heggie (22) investigated the percutaneous penetrability and drug carrier potentials of DMSO in guinea pigs and rabbits to determine if topical application of 1-methyl-2-hydroximinomethylpyridium methane sulfonate (P2S) in DMSO could produce effective plasma levels to protect against poisoning by the anticholinesterase sarin (isopropyl methylphosphonofluoridate). Normally, plasma clearance of P2S is within 2 hours after the intramuscular injection of 60 mg/kg to guinea pigs. When P2S in DMSO was applied topically to guinea pigs, P2S was detected in the plasma for as long as 11–12 hours. The authors believe that this long duration of P2S in the plasma is either due to its slow but continuous passage through the skin or to DMSO interfering in some way with the metabolism or excretion of P2S.

Horita & Weber (23) studied in mice DMSO-induced enhancement of absorption of 5% d-tubocurarine, thiopental, reserpine, chlorpromazine, pheniprazine, and tranylcypromine in undiluted DMSO. The behavior of the

mice was noted before and after immersing their tails in the drug solutions 3–4 times for 30-second periods at 10-minute intervals. The onset of systemic action with behavioral changes usually appeared within 60–70 minutes after the first immersion. With d-tubocurarine, however, signs of muscle flaccidity appeared after two applications and these animals died from paralysis of the respiratory muscles 10 minutes after the fourth tail immersion. Comparisons were made also for skin penetrability and drug carrier ability of DMSO and other solvents. The drug tested was a 5% solution or suspension of d-tubocurarine in DMSO, or in N,N-dimethylformamide (DMF), ethyl alcohol (strength not given), acetone, propylene glycol, or water. The average time intervals between the first tail immersion and death from respiratory paralysis were: DMF, 35 min; water, 47 min; DMSO, 49 min; acetone, 64 min; propylene glycol, 65 min; and alcohol, 67 min.

Franz & Van Bruggen (24, 25) measured the flux of electrolytes and radioactive nonelectrolytes through the abdominal skin of *Rana pipiens*. When 2.5% DMSO was added to the outer (epidermal) electrolyte solution bath, the potential difference between the two solutions was decreased. Addition of 2.5% DMSO to the outer bath greatly increased the flux of radioactive thiourea, urea, mannitol and sucrose. The marked increase in frog skin permeability to nonelectrolytes apparently involves two mechanisms: hypertonicity leading to a nonselective increase in permeability of the skin and, to explain the increase in the rate of movement of molecules across the skin only in an inward direction which becomes greater as the size of the tracer hyperosmolar molecule increases, "an interaction between the movement of DMSO across the skin and the movement of the tracer species."

Kolb (26, 27) studied the rate of cutaneous penetration and absorption of 90% ^{35}S- and ^{3}H-labeled DMSO in rats by measuring radioactivity of the blood in arteriovenous shunts. The maximum impulse count was registered 10 minutes after the dermal application at which time the blood concentration of DMSO was 18 mg%. The half-life of DMSO in the blood was more than 10 hours. In beagles following the application of the radioactive DMSO, the count in the blood increased slowly, plateaued at 45 minutes and remained almost unchanged at 8–12 mg% for 7 hours. Cutaneous resorption was estimated by excising and analyzing the treated skin after one application of DMSO. Four hours after application, 80% of the DMSO had penetrated the skin while after 24 hours this amounted to more than 90%.

A remarkable amount of radioactivity was found by Hucker et al (28, 29) in the plasma of rats and rabbits sacrificed after cutaneous applications of DMSO-^{35}S (0.55 g/kg, approximately 0.5 μc). The maximal level was reached 2 hours after dosing. In rats the tracer DMSO rapidly penetrated the skin with 63% of the original dose remaining at the site of application after 30 minutes; 19% after 1 hour; and 14% (average) after 2 hours. After 24 hours the radioactivity at the site of application was the same as that of the surrounding skin. A greater amount of DMSO penetrated the rabbit's skin with 85% found at the application site after 30 minutes and 11%

(average) after 4 hours. Absorption was completed after 24 hours.

Percutaneous absorption in man.—Herschler & Jacob (6) were the first investigators to use dermal applications of undiluted chemical grade DMSO clinically. Further clinical trials with DMSO in the treatment of musculoskeletal disorders were carried on by Jacob & Rosenbaum (30). Kolb (27) applied 90% DMSO-^{35}S to the skin of volunteers and found radioactivity registered in the first blood sample drawn 5 minutes after administration. A maximal blood concentration was reached between the 4th and 6th hour after application and remained constant for 1½–3 days. After a dose of 2 g DMSO-^{35}S applied cutaneously, from 10–15% of the tracer was excreted in the urine over 24 hours and about 40% was eliminated during the first week. Epidermis scraped from the area of application 8 hours after a dose of 2 g DMSO given to one volunteer showed a radioactivity value of about 20% of the administered dose. Later, Kolb (26) reported that elimination of radioactive DMSO in the breath after cutaneous application of 2 g DMSO was 1% during the first 6 hours and for 24 hours it was 1.5 and 3% (31). Dimethyl sulfide, determined by gas chromatography of the exhaled air, amounted to 4 and 9 mg during the first 6 hours while at 24 hours after cutaneous application no DMS was found in the breath.

Hucker et al (32) used gas chromatography for analysis of DMSO and dimethylsulfone ($DMSO_2$) in the serum and urine of man. Dermal administration of 1 g/kg of DMSO-^{35}S to two subjects gave maximal serum levels of DMSO 4 to 8 hours after treatment. These levels then declined and 36–48 hours after application no DMSO was detected. The dimethylsulfone levels lagged behind those for DMSO, becoming maximal after 36–72 hours and then gradually declining but still detectable after 312 hours. Urinary excretion of DMSO began shortly after dermal administration in both subjects and over 48 hours when excretion was completed, it averaged 13% of the dose. Dimethylsulfone excretion did not become significant until 8 hours after dosing but continued for 456 hours. The average total amount of $DMSO_2$ excreted was equivalent to 17.8% of the DMSO dose. Thus, 30.8% of the dose was accounted for as DMSO or $DMSO_2$.

Kligman (33), using specimens of human skin, has convincingly demonstrated the potent dermal penetrability and carrier ability of DMSO. He obtained the fastest and greatest penetrability of dyes, corticosteroids, and other pharmacological agents through skin with 70–90% DMSO.

Penetration of mucous membranes.—The pioneer study by Jacob, Bischel & Herschler (34) demonstrated the penetrability and carrying capacity of DMSO across the mucous membrane of the dog's bladder. A "basic solution" containing sodium salicylate, sodium sulfadiazine, Evans Blue dye, and sodium heparin was instilled into the bladder and blood samples taken at 30, 60, 120, and 240 minutes. Compared to saline controls addition of 15% DMSO produced a significant increase in clotting time, a six- to eightfold increase in serum sulfadiazine, and a two- to fourfold increase in serum

salicylate. At autopsy, the Evans Blue dye was found in the peritoneal tissues.

Recent in vitro studies[2] show that the transport of ^{45}Ca-labeled calcium with ^{14}C-labeled DMSO from the mucosal to serosal side of an intestinal sheath increases as the concentration of DMSO increases.

Distribution.—Following dermal, oral, and intraperitoneal administration of DMSO-^{35}S to rats and rabbits, significant radioactivity appeared in various organs within 30 minutes (29). After oral or intraperitoneal treatment, maximal plasma concentrations were reached in from 0.5–1 hour and then decreased to one-half this peak value at 6 hours and to only 5–10% of the maximal concentration at 24 hours. After oral administration concentrations of DMSO in the organs of rats and rabbits dropped rapidly during the subsequent 24 hours.

Metabolism.—Four hours after oral DMSO-^{35}S in rats the ratio value for dimethyl sulfone ($DMSO_2$) was 6.5% of that for DMSO in the plasma, liver, testes, kidney, spleen, small intestine, and heart (29). After dermal administration of DMSO-^{35}S to rabbits, the $DMSO_2$/DMSO ratio was 11.6% in the testes, brain, plasma, bile, aqueous humor, lens, vitreous humor, and skin at the site of application. A higher ratio was found in the liver and kidneys. After cutaneous administration of DMSO-^{35}S to man, DMSO disappeared from the blood in 30–48 hours. Serum $DMSO_2$ reached peak values after 36–72 hours and had disappeared after 312 hours (32, 35). Denko et al (36) believe that the sulfur atom in DMSO follows the same metabolic pathways as organic sulfur. The organic sulfur in ^{35}S-labeled methionine and cystine is metabolized mainly in soft tissues and muscle, being used chiefly for protein synthesis. In rats, DMSO-^{35}S also concentrated in soft tissues, such as the stomach, spleen, and brain. With respect to the metabolism of sulfides, such as dimethyl sulfide, in vivo oxidation takes place through a sulfoxide intermediate with further oxidation to sulfones (37–39). Dimethyl sulfone is apparently a normal metabolite as it has been isolated from beef adrenals (40), beef blood (41), normal human urine (42), and cow's milk (43). Also, dimethyl sulfide has been found as a natural constituent in cow's milk (44).

Excretion.—After 24 hours urinary excretion of DMSO-^{35}S following intravenous dosing in rats was 80% of the total dose compared to 65–75% when topically applied (29) and 52% after intraperitoneal injection. However, Malinin et al (45) collected only 30% of the radioactive DMSO given intraperitoneally to guinea pigs. In dogs, the oral or intravenous administration of DMSO resulted in the urinary output of 50% of the dose in 36 hours (26, 27). Examination of 24-hour urine collections after intraperitoneal injections of DMSO-^{35}S to rats disclosed a recovery of 12.8% as dimethyl

[2] P. K. Dea and S. I. Chan, Personal Communication to R. J. Herschler and S. W. Jacob, March 1971.

sulfone (29). In man, dermal administration of DMSO-^{35}S showed that all the DMSO had been excreted within 48 hours while $DMSO_2$, first noted 8 hours after treatment, continued to be excreted for 480 hours (32, 35). A total of 13% of the dose appeared in the urine as DMSO and about 18% as $DMSO_2$. Following oral administration, the urine recovery of DMSO was 50.8% and 22% for $DMSO_2$. Kolb et al (26, 27) recovered 80% of the original dose of DMSO within 8 days after intravenous administration to man but only 50% over a 10–15-day period after cutaneous application. These workers noted that man excretes very little DMSO in the feces.

No adequate explanation has been offered for the failure to account for the recovery of more than approximately 80% of the total dosage of DMSO administered. Rammler et al (21) offer schematic formulas to support their suggestion that DMSO may undergo both oxidative (to dimethyl sulfone) and reductive (to dimethyl sulfide) reactions in its complete metabolism to sulfate. These investigators theorize that if sulfate is, indeed, one of the end products of oxidation of DMSO, its accumulation in high concentrations in the eye (46) might explain the ocular effects noted after prolonged administration of large doses of DMSO in animals (47).

Toxicity

Table 1 summarizes the acute single dose toxicity of DMSO in animals. Similar data are offered by Mason (48) and Smith et al (49). Although some spread in the range of LD_{50} values is noted for each route of administration, the values for mice and rats show little differences.

Chronic toxicity studies have been made for a number of routes of administration using various concentrations of DMSO. Dermal application of 100% DMSO to backs of guinea pigs in 28 daily applications and to hairless mice given two applications a week for 30 weeks caused no skin irritation and no toxicity (49). Although little skin irritation appeared when Brown and his associates applied 10 ml 100% DMSO to the backs of rabbits 15 times in 20 days, at the end of the test the treated skin was dried, cracked, and scaly (50). Jacob (51) reports no significant abnormalities in a battery of blood chemistry, hematology and urine studies when 1 g/kg DMSO was applied to the backs of dogs 5 days a week for 18 months. Similarly, in both monkeys and dogs various laboratory determinations remained normal for 6 months with weekly applications of 3.3–33 g/kg of 60–100% DMSO to the shaven skin of the back according to Smith et al (49). However, beginning within 3 weeks and persisting throughout treatment, the skin in both species became "furfuraceous" and desquamated. Sommer & Tauberger (52) noted that oral administration to rats of 2 ml/kg/day of 20% DMSO and 8 ml/kg /day of 80% DMSO for 13 weeks was tolerated while 16 ml/kg/day as an 80% solution given to 20 rats killed 2 animals in 24 hours and 10 by the 28th day of treatment. Caujolle and his group (53) fed rats 2 g/kg 100% DMSO for 45 days with no untoward effects while 5 g/kg of 50% DMSO for the same period of time resulted in a slight weight loss and histopathological evidence of liver damage. Jacob (51) reported that two dogs given

TABLE 1 SINGLE DOSE TOXICITIES (LD_{50}) OF DIMETHYL SULFOXIDE

Species	Dose and *Reference	Routes of Administration				
		Dermal	Oral	Subcutaneous	Intraperitoneal	Intravenous
Mouse	g/kg	<50	16.5, 21.4, 28.3	13.9, 15.3, 20.5	14.7, 17.7	3.8, 5.7, 7.6, 8.8, 9.2
	Ref.	49	52 57 49	52 53 55	[d] 53	55 57 49 [e] 53
Rat	g/kg	<40[a]	17.8, 20, 19.7, 28.3	12 13.5, 20.5	>5, 12.9	5.2, 5.3, 8.1
	Ref.	48	[f] 50 52 56	52 53 55	50 53	55 56 52
Guinea Pig	g/kg		11		5.5	
	Ref.		50		50	
Rabbit	g/kg					19.2[b]
	Ref.					53
Cat	g/kg				>4	4, 4
	Ref.				103	103, 49
Dog	g/kg	>11	>10[c]			2.5, 2.4
	Ref.	49	51			55 56
Monkey	g/kg	>11	>4			>11
	Ref.	49	54			54

* Reference source placed below value.

[a] Body, except head, dipped into 100% DMSO.

[b] Unanesthetized, 40% DMSO perfused at rate of 90 ml/hr with average survival time of 92 minutes.

[c] As 33% solution.

[d] Farrant, J. 1964. *J. Pharm. Pharmacol.* 16: 472–83.

[e] Caujolle, F., Caujolle, D., Bouysson, H., Calvet, M. M. 1964. *C. R. Acad. Sci.* (Paris) 258: 2224–26.

[f] Crown Zellerbach Tech. Bull. 1964. *Report M-543, Lab. Vitamin Technology*, Chicago, Aug. 1, 1955.

2.25 g/kg of DMSO as a 15% solution by stomach tube once weekly for 3 weeks showed no significant changes in blood, urine, or liver profile examinations over the next 8 months. Smith's group (49) started three dogs on a daily dose of approximately 2.5, 5, or 10 g/kg of DMSO given orally first as a 50% solution and then, after several days, as a 25% solution. One dog died after 14 days, having received a mean daily oral dose of 5.3 g/kg; at terminus the hemoglobin, hematocrit and SGOT, and SGPT were elevated. The other two continued treatment with one receiving 5 g/kg for 35 days and the other 3.8 g/kg for 48 days (at which time slit lamp examinations revealed faint anterior and posterior cortical bands in the lens of each eye). Further treatment of both dogs with 10 g/kg/day for 13 more days caused myopic changes and further lenticular changes in the eyes of both dogs. The hematology and blood chemistry determinations were normal. Feinman et al (54) gave dogs oral doses up to 4 g/kg of DMSO for 5 consecutive days which were tolerated.

Both intravenous and intraperitoneal injections of various tions of DMSO were surprisingly well tolerated. Rosenkrantz et al (55) found that intravenous doses of 2.5 g/kg/day of 100% DMSO could be given for only 15 days to rats since necrotic lesions at injection sites pre-

vented further trial. These workers also gave dogs intravenous doses of 0.4 g/kg daily for 33 days with no deaths, although at necropsy fatty changes were seen occasionally in the central portion of the liver lobule. In another study Willson and associates (56, 57) gave intravenous doses of 0.3 g/kg/day to dogs using 100% DMSO for the first 10 injections, the next 3 as 67% DMSO, and subsequent injections as 50% DMSO because of occlusion of the veins. However, injections of 10 or 25% solutions of DMSO in 5% dextrose to dogs at dosages of 0.3 g/kg/day for 24 days did not cause intravascular thrombi. Feinman et al (54) found that two monkeys survived 69 intravenous infusions of 4 g/kg of DMSO given 5 days a week. Intraperitoneal injections of from 0.5 to 8 g/kg/day of DMSO for 24 days were survived by rats but the highest dose caused hemolytic anemia in these animals. Also, the different dosages of DMSO led to varying degrees of organization and widespread adhesions of the peritoneum (56, 57). Caujolle's group (53) observed that intraperitoneal administration of 1, 2, and 5 g/kg of DMSO daily for 6 weeks in rats did not induce gross toxic signs although necropsy revealed histological evidence of disseminated areas of necrosis in the viscera. Similar results were noted when 2.5 to 5 g/kg of DMSO was given intraperitoneally daily for 30 days to rats by Smith et al (49). One explanation for the relative lack of injury to the tissues when moderately large doses of DMSO were given subcutaneously may be its rapid absorption from the tissues. No deaths occurred in rats given 2.5–5 g/kg/day subcutaneously for 30 days (55). But the larger dose of 10 g/kg/day could be administered subcutaneously to rats for only 15 days as necrotic lesions developed at injection sites. Salmon and trout have been given intraperitoneal injections to establish the LD_{50} which ranged from 12–17 g/kg (58). Kept in tanks, these fish tolerated 2% DMSO for 100 days but in a 4% solution, erosions developed in the gills while at 4.6% the fish lived for 96 hours or less.

No cumulative effects or increased toxicity resulted with repeated daily dosing when the daily dose did not exceed the single maximum tolerated dose and the concentration of DMSO remained under 50%.

Teratogenicity.—Caujolle et al (53) injected a near-LD_{50} dose of 50% DMSO in 0.9% saline into 72-hour and 96-hour chick embryos. Examination of the 324 surviving 72-hour embryos on the 10th–16th day of incubation disclosed that 18.5% had malformations of the eye or upper beak. Of the 436 surviving 96-hour embryos, 25.9% showed deformities affecting mainly the limbs (ectromelia, brachymelia, phocomelia). The 278 embryos injected with saline at 72 or 96 hours apparently did not show any greater incidence of malformations than the usual 2% which occur spontaneously. Mice and rats were given intraperitoneal injections of from 5 to 12 g/kg of 50% DMSO from the 6th–12th day of gestation. Seven of the 100 mice foetuses obtained near or at term were deformed, as were 11 of the 729 rat foetuses. Malformations noted were anencephalia, microphalia, celosomia, edema, and limb, jaw, and tailbud deformities. Only 1 malformed foetus of

83 foetuses was obtained from rabbits on the 20th–24th day of gestation after treatment with 5 g/kg of DMSO orally, or 4 g/kg subcutaneously, on the 6th–14th day of gestation. While Montouri & Adler (59) found that a high incidence of mortality and teratogenesis resulted from injection of DMSO into the chicken embryo they pointed out that inert substances such as talc, animal carbon, or "pieces of skull" are teratogenic to the egg embryo. Ferm (60) injected 2.5–15 g/kg of 100% DMSO intraperitoneally in pregnant hamsters with the highest dosage killing 25% of the embryos and causing exencephaly and anencephaly in 100% of the surviving foetuses.

Boost, in a personal communication (Oct. 10, 1965) to the author, reported on 50% DMSO given orally at a level of 5 g/kg/day to male and female rats for 4 days prior to mating. Fertility was judged to be normal. The pregnant females were then given DMSO throughout the gestational period. All litters were regarded as normal and the young rats developed in a normal fashion.

Ocular toxicity.—Interdiction of clinical trial of DMSO in November 1965 followed reports that DMSO had caused eye damage in animals (61). Rubin and his associates (62, 63) made repeated slit lamp examinations on dogs given oral doses of 2.5, 5, 10, 20, and 40 g/kg/day of DMSO for 5 days a week. During the 9th week of treatment they noted lens abnormalities in 2 dogs given 5 g/kg/day of DMSO, in 1 dog getting 10 g/kg/day, and in 1 dog of 2 which were initially started on 40 g/kg, withdrawn for 5 days at the end of the 2nd week, restarted on 20 g/kg twice daily during the 3rd week, and then continued on 10 g/kg twice daily. By the 13th week 1 dog of the 2 started on 2.5 g/kg/day showed ocular changes while the other showed these by the 18th week. Slit lamp biomicroscopy and, later, direct ophthalmoscopic examination disclosed that the otherwise normally translucent and homogeneous lens was divided into two distinct zones. The central portion appeared as a nucleus and became clear leading to as much as a −20 diopter decrease (myopic) in the ophthalmoscopic lens setting. The cortical zone also was clear and had lost its normal relucency. Usually, lens changes were bilateral, appeared to be dose-related as to severity and time first observed, and eventually appeared in most of the treated animals. In another experiment this group (63) found that regression of the lens lesions may take place whether or not DMSO treatment is continued.

In a comprehensive study Wood et al (64, 65) found by slit lamp examination that oral or cutaneous administration of 100% DMSO to rabbits in a dosage of 10 g/kg/day revealed "well-defined lines of discontinuity in the lens" at the end of the first or second week. With continued treatment haziness developed in the central nuclear region and after 4–5 weeks the lens became dense and myopia had developed. At the end of 10 weeks the animals were sacrificed. Dissection of the lenses from two orally treated young rabbits showed a normal cortex but an unusually firm, although still clear, nucleus that shelled out. Chemical assay of the lenses from both orally and topically treated animals showed slight reductions in the concentrations of urea, glutathione, uric, and amino acids, and of the soluble lens proteins

with a reciprocal increase in the insoluble proteins. Gamma crystallin of the soluble lens component accounted for most of the decrease. Because gamma crystallin is rich in sulfhydryl groups and higher concentrations of it are found in the lens nucleus than in the cortex, "these sulfhydryl groups could readily enter into oxidation-reduction reactions with DMSO." Another possibility is that DMSO could lead to the binding of some protein-SH groups that would alter protein structure.

Other investigators (48, 66, 67) have observed lenticular changes in dogs following oral or cutaneous administration of large doses of DMSO. Mason (48) reports that repeated dermal application to dogs of DMSO in doses as high as 11 g/kg/day resulted in "a progressive and marked myopia (that) developed in 8 weeks and a nuclear haze after 10 weeks."

Radioactive techniques have been used to study the concentration and to demonstrate the accumulation of DMSO in ocular tissues (46). Denko and associates (36) administered DMSO-^{35}S cutaneously and intraperitoneally to rats that were sacrificed 2 hours later. Examination of their tissues showed the vitreous humor and scleral coats of the eye to have as high radioactivity as the soft tissues. The lens, however, showed low levels. When the rats were sacrificed 6 hours after DMSO-^{35}S administration, low levels of the isotope were found in the vitreous humor and scleral coat indicating that DMSO leaves these structures rapidly. Chronic administration of radioactive DMSO in dogs and rabbits led to higher levels of DMSO in the vitreous humor and scleral coats than in soft tissues (27).

Mason (48) gave 8 monkeys 11 g/kg/day of 90% DMSO dermally for periods of 168–175 days. The average refractive change was 0.66 diopters, no myopia was measured, and "only one (monkey) showed a trace of cortical banding" in the lens.

In man, Gordon (68) treated 108 patients diagnosed as having ocular disorders, intraocular inflammatory diseases, and allergic states, with topical DMSO applied over periods of from 1–15 months. Concentrations of DMSO mixed with tetrahydrolazine (Visine®) ranging from 7.5–66% were used. No changes were noted by repeated ophthalmoscopic and slit lamp examinations. None of the eyes showed any evidence of corneal injury when tested with fluorescein. Seventeen patients with lens opacities diagnosed as "clinical cataracts" prior to DMSO treatment showed no increase in this condition during therapy. Jacob & Wood (69) reviewed published data with complete ophthalmoscopic examinations both before and after topical treatment with DMSO and found no ocular toxicity. Two other clinicians (70, 71) made serial ophthalmoscopic examinations on patients treated topically with DMSO for an average of two months and noted no eye changes. Recently, Hull, Wood & Brobyn (72) did a series of ocular examinations on 38 male prisoners before, during, and for one year following daily application of 80% DMSO gel for 12 weeks. Another 18 inmates treated with a nonmedicated gel and kept segregated were observed in a similar manner. No statistical differences in the ocular examinations and measurements were found for the two groups.

Adverse reactions in man.—Immediate stinging and burning followed by mild erythema and itching lasting an hour or so occurs in most persons applying 70–90% DMSO dermally. After a few days of continued application of DMSO in most patients, this reaction lessens. Cutaneous applications two or three times a day in the same area for several weeks may lead to mild scaling and drying of the skin. Kligman (33) believes that the erythema is due to histamine release, tolerance developing rapidly from depletion of histamine in the mast cell stores. Contributing to the erythema may be the exothermic association of DMSO with water leading to increased vascular permeability (73, 74). Brown (75) noted that 15 of 25 patients being treated with daily doses of 15 to 45 ml of 80% DMSO gel complained of either moderate or marked skin reactions to the drug. Kligman (33) and others (69–71) found no remarkable changes in hematology, blood chemistry, and urinalyses when these determinations were done repeatedly in patients treated with topical DMSO.

PHARMACOLOGY

Jacob and his associates (9, 69) list a number of primary pharmacologic effects of DMSO.

Analgesia.—Pain relief from dermal administration of DMSO to affected areas seems to involve more than local analgesia, anti-inflammatory action, or vasodilation. Cutaneous application of DMSO at some distance from the affected site usually relieves pain and inflammation in the latter location, suggesting that DMSO either has been carried by the circulation to the affected area to act locally or has depressed the central nervous system pain centers—or both. In laboratory studies[3] application of DMSO to the neck of a rat elevates the "squeak threshold" when pressure is applied to a carrageenin-injected inflamed hind paw using Randall & Selitto's (76) method. Phatak & Cruz[4] employed the radiant heat-rat tail technique for testing for analgesic effect and obtained significant analgesia with dermal application of 90% DMSO alone. Application of 20 mg/kg morphine sulfate in 50% or 100% DMSO did not elicit an analgesic effect but very significant analgesia was achieved with 20 mg/kg morphine sulfate in 90% DMSO. Dermal doses of 100 mg/kg of morphine sulfate in 90% DMSO were equivalent to subcutaneous injections of 2 mg/kg morphine sulfate in saline when tested by this technique.

The conduction velocity of the isolated frog's sciatic nerve was decreased 40% by immersion for several hours in 6% DMSO (77, 78). Other studies (79) done on isolated sensory nerve fibers of the cat indicate that the "C" unmyelinated fibers are completely depressed within one minute in 5 to 10% concentrations of DMSO. Kligman (33) obtained partial anesthesia to pinpricking when 0.1 ml of 50% DMSO was injected intradermally in his prisoners.

[3] Informational Material on Dimethyl Sulfoxide (DMSO), Merck Sharp & Dohme Research Laboratories, West Point, Penn., Sept. 1, 1964.

[4] N. M. Phatak and A. J. Cruz, unpublished observations, 1969.

Central nervous system effects.—Several investigators have observed a sedative effect in both man and animals following large doses of DMSO (49, 69). Braude & Monroe (80–82) gave intraperitoneal injections of 5 g/kg of DMSO to mice and found a decrease in the spontaneous motor activity and an increase in the hexobarbital sleeping time. Rosenbaum et al (83) report that 17 of 548 patients treated cutaneously with DMSO complained of increased fatigue and lethargy, which disappeared a few days after stopping DMSO. Ramirez & Luza (84) gave intramuscular injections of 5 ml of 80% DMSO two or three times a day to 42 severely disturbed psychiatric patients. They felt that DMSO had antipsychotic and antianxiety properties and that its action differed from tranquilizers in that little sedation or central depression was produced.

Anti-inflammatory activity.—The investigators[3] who found some analgesic effect from dermal application of DMSO noted that 1 ml/kg DMSO to the back of the rat's neck one hour before subcutaneous injection of carrageenin into the plantar surface of a hind paw resulted in 31% inhibition of foot edema. A greater inhibition occurred when DMSO was given orally with 1 mg/kg effecting 22% inhibition, 2 ml/kg a 42% inhibition, and 5 ml/kg, 46% decrease in edema. Cotton pellet implantation in rats and dermal application of 0.2 ml DMSO per rat daily for 7 days led to a 27% inhibition in the weight of the granuloma formed. Formanek & Kovac (85) in similar studies observed that DMSO increased the infiltration of leukocytes into the traumatized area of pellet implantation and suggest that the decreased formation of granulation tissue is due to an anti-inflammatory action. They also found that cutaneously applied DMSO reduced experimentally produced edema of the rat's paw. Dimethyl sulfoxide possessed potent anti-inflammatory properties when used to treat adjuvant-induced polyarthritis in rats (86, 87). Clinically, some success was encountered with topical application of 70% DMSO in inhibiting experimentally produced contact dermatitis, allergic eczema, and skin calcification in the rat (88). In in vitro studies Weissmann & Thomas (89) found that addition of DMSO to cortisone, cortisone acetate, cortisol, prednisone, and chloroquine lowered the concentrations of the corticosteroids required to effect the release of beta-glucuronidase and acid phosphatase from lysosome-rich fractions of rabbit liver.

A later manifestation of inflammation is fibroblast proliferation. Berliner & Ruhmann (90) report that the growth of tissue culture fibroblasts was not inhibited when exposed to 1% DMSO but 3% and 5% concentrations of DMSO did depress fibroblast growth 3, 5, and 7 days after inoculation. Concentrations of cortisol of 0.01 μg/ml did not suppress fibroblast growth unless combined with 1% DMSO.

Effect on collagen.—Collagen deposition occurs in the formation of intestinal adhesions and other inflammatory repair processes. Mayer et al (91) abraded a 4–5 cm segment of distal ileum of the rat along the mesenteric border with gauze until most of the serosal layer was wiped off. This

led to development of adhesions in 100% of the control rats within 30–35 days. But, when daily intraperitoneal injections of the following agents were given postoperatively for 35 days, the incidence of adhesions was: DMSO (1 g/kg/day), 20%; DMSO-cortisone, 80% incidence; cortisone (2.5 mg/kg/day), 100%; and saline solution, 100%. Scherbel and coworkers (92) have achieved excellent clinical results in most of their scleroderma patients treated topically or subcutaneously with DMSO. Urinary excretion of hydroxyproline, a component of collagen, showed marked increases in the 24-hour urinary levels during the first week of treatment in 6 of 21 patients treated with DMSO and during the first month the average increase was 50% above the average pretreatment urinary output of hydroxyproline. Repeated skin biopsies of the sclerodermatous area on 9 of these patients showed increased amounts of acid mucopolysaccharide from broken-down collagen.

Antipyretic activity.—Subcutaneous injection of 2 ml of 7.5% suspension of brewer's yeast in rats elicits a persistent fever. Oral administration of antipyretic drugs promptly reduces the fever in a dose related manner. Application of DMSO to the back of the neck of the rat did not have an antipyretic effect,[3] but Jacob in a personal communication reports on antipyretic effect of parenteral DMSO in rodents and dogs.

Cardiovascular and respiratory effects.—Pentobarbitalized cats given intravenous dosages of 33 and 66 mg/kg of 100% DMSO showed transient blood pressure increases of +26 and +40 mm Hg (50). Other workers (93) found that initial intravenous dosages of 200 mg/kg of undiluted DMSO produced apnea in the cat but subsequent dosages of the same magnitude did not. Blood pressure and heart rate fell transiently after intravenous administration of 200 mg/kg of DMSO. Vagotomy did not alter the DMSO-induced hypotension and bradycardia but 1 mg/kg atropine did modify these effects somewhat.

Peterson & Robertson (94) gave anesthetized dogs successive dosage increments of from 5 to 10,000 mg/kg DMSO as a 25% solution by intravenous infusion. Some pressure changes were noted but they were attributed to the high osmotic load injected rather than to any specific cardiovascular effects.

Diuresis.—The diuresis resulting from dermal or systemic administration of DMSO first reported by Jacob et al (9) depends on the total amount of DMSO administered. In cats, DiStefano & Klahn (93) gave intravenous or intraperitoneal injections of 100% DMSO in repeated dosages of 200 mg/kg at 15-minute intervals, doubling the dosage when a total amount of 1 g/kg had been given intravenously or 5 g/kg intraperitoneally. They found the increase in urine output paralleled the total amount of DMSO given, rather than the degree of dilution reached. They suggest that DMSO "may be exerting an osmotic diuretic action." Formanek & Suckert (94a) adminis-

tered 0.5 ml of 90% DMSO topically to rats five times daily which increased the urine volume tenfold, and also increased both sodium and potassium excretion. Similar results were obtained with oral DMSO.

Vasodilation.—Kligman (33) observed that DMSO possesses potent histaminelike properties at the site of cutaneous application, resulting in an increased blood flow to the skin. Adamson et al (95) prepared dorsal pedicle flaps on the backs of rats. These flaps have a length to width ratio of 3:1 and are elevated on three sides from the distal base. In untreated rats a consistent slough of approximately 40–50% of the distal end of the flap occurs. When 6 ml of 70% DMSO were sprayed on the flap skin area three times daily for 32 days, only minimal slough of the distal portion of the flap resulted. With use of the smaller dose of 4 ml of 70% DMSO, flap slough occurred more noticeably with about 15–20% of the distal portion involved. These results were attributed to the "histaminelike action of the drug in addition to its strong hygroscopic and other anti-edema properties." Kappert (96) has used 15% DMSO as a carrier for substances such as linoleic acid, vitamin A or azulene in spray form, or a "tincture" or ointment of 70% DMSO containing "a membrane-obturating P factor" in the treatment of vascular diseases. Cutaneous application of these preparations benefitted patients with post-thrombotic syndrome, Raynaud's disease, scleroderma, and brachialgia. The author concludes that these effects are due to the anti-inflammatory, analgesic, mild bacteriostatic action; the facilitation of penetration and absorption of other drugs; and the vasodilatory effects of DMSO. Brown (75) considers the vasodilatory action of DMSO upon the vascular tree proximal to the area to which it is applied as one of the important therapeutic effects of DMSO.

Cholinesterase inhibition.—In addition to their studies on the frog sciatic nerve, Sams et al (77, 78) showed that DMSO depressed the vagal threshold to electrical stimulation in the isolated innervated guinea pig atrium and led to the production of spontaneous fasciculations of the isolated guinea pig diaphragm and suggested that these effects are due to cholinesterase inhibition. Additional support for this hypothesis was provided by an in vitro assay experiment which showed that 0.01, 0.1, 0.5, and 1 molar DMSO inhibited bovine erythrocyte cholinesterase 3%, 16%, 44%, and 85% respectively (97).

Smooth muscle activity.—According to Bonnardeaux (98) DMSO, formamide and propylene glycol cannot be considered as inert solvents when used with other agents in vitro or in vivo. He recorded the spontaneous activity of fresh strips of the rat's duodenum, rectum, and uterus mounting the lumens in the classical method to record longitudinal axis forces and, also, in an offset manner to record both longitudinal and circular smooth muscle changes. Each of the solvents depressed the amplitude of the contractions and with DMSO this effect was attributed to metabolic changes

induced in the muscle fibers. The changes these solvents effected in the frequency of contraction of the duodenum were thought to be due to direct membrane phenomena and nervous interaction, while the changes in activity of the uterus and rectum appeared to be directly, or indirectly, due to metabolic action. Einer-Jensen (99) recorded the spontaneous isotonic contractions and electrical activity of 3 cm sections of pregnant rat uteri in an organ bath using platinum wire electrodes set 2–3 mm apart to record electrical changes. Addition of 0.17% DMSO to the uterine strips in the bath elicited minimal changes in electrical activity and contractions. But progesterone dissolved in DMSO (50 mg/ml) promptly stopped the contractions although only minor changes were noted in electrical activity. These effects were reversible after washout. Earlier studies[3] of the effect of DMSO on the gastrointestinal tract showed that oral administration of the solvent did not inhibit rat gastric secretion, did not stimulate acid secretion from either the stomach or gastric fistula pouches in the dog, and did not block histamine-stimulated or food-stimulated gastric secretion in dogs. In starved rats, stomach tube administration of 20 1 mm diameter pellets after 1 mg/kg DMSO orally did not inhibit the stomach emptying time. Only a slight depression of intestinal propulsive activity was observed in mice given a charcoal meal after 1 ml/kg DMSO orally.

Bacteriostasis.—It would be expected that solvents like alcohol (100) and acetone (2) would possess some antibacterial action. In preliminary screening studies Jacob et al (9) found 20% DMSO bacteriostatic against *E. coli, Staph. aureus,* and *Pseudomonas* and, in 5% concentration, against the tubercle bacillus. Kligman's (101) extensive studies in the laboratory and on human subjects found 20% DMSO bacteriostatic against a number of "normal skin residents." When 1 ml of 90% DMSO was applied topically in the axilla 3 times daily for 3 days, the bacterial population was considerably lessened (90% reduction). Kligman found DMSO a weak antifungal agent, which might be more effective when topical fungicides are incorporated in it. Alone, 90% DMSO swabbed twice daily between the toes resulted in moderate clinical improvement in 8 of 11 subjects with tinea pedis. In early toxicity studies (49, 52, 55) subcutaneous or intramuscular injections of DMSO caused local tissue reactions with hemorrhage and inflammation but "no instances of abscess formation, necrosis, or sloughing were reported" (48). While some facets of the meticulous investigation carried out by Seibert and her associates (102) in isolating, identifying, and growing pleomorphic types of bacteria from the blood of leukemia patients and from cancer tumor specimens may be open for speculation, their use of DMSO to suppress growth of these organisms is convincing. They added lysozyme and d-ethambutol Cl to various cultures of pleomorphic organisms, including atypical mycobacteria, and obtained only partial inhibition in most cultures. DMSO in a 12.5% or 25% concentration, "because of the phenomenal penetrating effect known for DMSO," was tested on organisms isolated from tumors and bloods from patients with cancer. While addition

of 12.5% DMSO completely inhibited 9 of 29 cultures tested and inhibited 8 more cultures to the extent of 75–90%, addition of 25% DMSO to 6 of these 8 cultures and to another 17 cultures resulted in 90–100% inhibition of growth. These concentrations of DMSO did not cause hemolysis or damage to suspensions of normal red cells. Jacob & Wood (31, 69) and Jacob (87) report Pottz's preliminary studies indicating that pretreatment of tubercle bacilli resistant to 2,000 μg of streptomycin or isoniazid with 0.5–5% DMSO rendered this organism sensitive to 10 μg of either drug. Kamiya et al (103) added 5% DMSO to culture media, which restored the sensitivity of antibiotic-resistant strains of bacteria to antibiotics and increased the sensitivity of those strains already sensitive to these agents. For example, DMSO restored the sensitivity of *Pseudomonas* to colistin. In addition, growth of *E. coli,* which is not affected by penicillin, showed growth-inhibitory effects when 5% DMSO was added to the culture. Jacob & Wood (69) mention the studies of Tsuchiya, Iriyama & Umezawa (104) who identified significant amounts of methylmethanthiosulfinate in DMSO-treated bacterial cultures, which they believe contributed to the antibacterial effect of DMSO. Or, according to Gillchriest & Nelson (105) DMSO may interfere with bacterial growth by altering the RNA conformational structure required for protein synthesis.

Drug interaction.—Anesthesia may sensitize cats to the lethal effects of large doses of DMSO, according to Smith et al (49), who had two of three unanesthetized cats survive an intravenous dose of 3 g/kg DMSO and one of three survive 6 g/kg to approximate an LD_{50} of 4 g/kg. This is in contrast to the maximum single intravenous dose of 0.4 g/kg of DMSO for anesthetized cats found by DiStefano et al (93). Braude & Monroe's (80–82) studies, already mentioned, showed that 5 g/kg of DMSO administered intraperitoneally to mice decreased spontaneous motor activity (SMA) and increased hexobarbital sleeping time (HST). When the almost insoluble anticonvulsant alphaglucochloralose (AGC) was dissolved in 25% DMSO and given intraperitoneally in mice the SMA and HST were increased significantly. However, no potentiation of the HST occurred. After performing a number of pharmacological screening tests, Dixon and his coworkers (106) found little evidence of drug interaction between DMSO and several commonly employed drugs. Determinations of LD_{50} for drugs such as chlorpromazine, morphine sulfate, pentobarbital, and ouabain in saline, or in 25% DMSO injected into mice, showed that DMSO did not increase the lethality of these drugs. DMSO did not significantly increase the LD_{50} for orally administered aspirin or benzylpenicillin. In contrast to the other studies[3] mentioned above, DMSO had little analgesic effect when tested by the Randall-Selitto paw method. Hexobarbital sleeping times were not altered when 2.5 g/kg of 25% DMSO were given subcutaneously to mice 1 hour, 24 hours, 7 days, or daily for 7 days prior to hexobarbital. Other examples of drug interaction have been offered by Melville et al (107) who report that DMSO enhances the action of digitoxin on the cat's heart without involving the myocardial fixation or degradation of the glycoside.

Other primary pharmacological actions of DMSO noted by Jacob (87) in his summary are: nonspecific enhancement of resistance to infection, muscle relaxation, antagonism to platelet aggregation, and lowering of cholesterol in experimental hypercholesteremia. The prophylactic radio-protective properties of DMSO are included (12).

Clinical Uses

Many of the large number of clinical studies reporting the various therapeutic uses of DMSO have been carefully conducted as well as critically and statistically evaluated by the investigators. These reports, together with firsthand clinical observation and trial of DMSO over many years, are sufficient to convince this writer of the unique efficacy and safety of this solvent in certain clinical situations. Reference has been made previously to some of these reports (31, 69, 71). The most recent report on the clinical use of DMSO in the treatment of acute musculoskeletal disorders is that of Brown (75). He compared the response to 80% DMSO gel, to 10% DMSO gel (placebo), or to standard therapy in a double-blind, controlled clinical study. Responses to therapy were graded employing chi-square contingency tables. Results reported were (*a*) in 15 patients with acute strains or sprains treated with 80% DMSO gel, an excellent response in 13 and a good response in 2. Nine patients treated with standard therapy had an excellent or good response; (*b*) in 30 patients with acute bursitis and tendinitis treated with 80% DMSO gel, the decrease in limitation of active and passive motion was significantly greater at 24 and 72 hours than noted in patients receiving standard therapy. The average number of days of work lost during the first week after injury was: treatment with 80% DMSO gel, 1.1 days; treatment with 10% DMSO placebo, 6.2 days; and, use of standard therapy, 3.1 days. As previously mentioned, 15 of the 25 patients treated with 80% DMSO had "either a moderate or marked skin reaction to the drug." In addition, 9 of these patients had either moderate or marked breath odor. Other types of acute musculoskeletal disorders due to athletic injuries have responded satisfactorily to topical application of DMSO (108–110). Continued dermal application of DMSO in patients with postoperative or posttraumatic intractable pain, postamputation phantom pain, and tic douloureux resulted in marked pain relief in 32 of 37 patients (111). For the first time through the use of DMSO it has been possible to offer some relief to scleroderma patients, particularly those incapacitated by contractures of the extremities, calcinosis, and skin manifestations of this obstinate collagenous disease (71, 92, 112). Topical administration of DMSO has been useful, probably through its bacteriostatic and vasodilatory effects, in healing skin ulcers and improving peripheral circulation in postthrombotic syndromes, and in Raynaud's disease, scleroderma, and brachialgia (96, 113). Jacob (114) found DMSO of value in the treatment of 60 patients with headache secondary to trigeminal neuralgia, sinusitis, cervical osteoarthritis, and temporal arteritis. Over 75% of the patients obtained relief when about 10–15 ml 50% DMSO were applied twice daily to the skin of the face and neck. If the headache was associated with sinusitis, 0.5 ml of 50%

DMSO was also instilled into each nostril. In addition to being helpful in the treatment of many different types of musculoskeletal, neurological, and dermatological disorders when applied dermally, DMSO has been found effective for a multiplicity of ailments when applied to mucous membranes, given orally or injected subcutaneously (99, 115, 116).

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