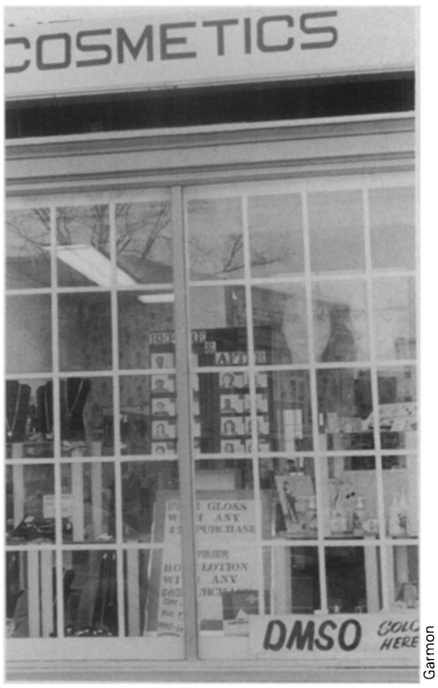
# Judging DMSO: There's the Rub

'Believers' rub on the industrial solvent DMSO for their aches and pains while the debate on whether it is safe and effective for such medicinal purposes continues



Garmon

By LINDA GARMON

The sign in the window of the cosmetic store says "DMSO sold here" to advertise the availability of this liquid chemical that has long been used as an industrial solvent. "I sell this stuff left and right; you wouldn't believe how much I sell," says the store's salesclerk. "People buy it for a hundred and one uses: arthritis, bursitis and muscle aches — anything having to do with pain," she says. DMSO is how her customers spell relief.

But DMSO also spells controversy—one generated over the question of whether the chemical is truly safe and effective in treating such muscle-skeletal problems and other disorders. The issue is nearly 20 years old and no longer burns with the passion that once had the chemical's proponents shouting "miracle drug" and its opponents screaming "hoax." Nonetheless, as reports presented at a fall New York Academy of Sciences conference and other recent events indicate, it still may be years before the complex controversy surrounding DMSO is resolved.

DMSO, or dimethyl sulfoxide ($Me_2SO$) has been a popular industrial solvent since the 1940s. The compound naturally occurs in trace quantities in a variety of fruits, vegetables, grains and beverages; commercially, it is produced by oxidizing (adding oxygen to) dimethyl sulfide.

DMSO's keen ability to penetrate the skin and to transport other chemicals with it into the bloodstream — a property that was discovered incidentally in its industrial use — suggested that it might have medical applications. So, in the early 1960s, human trials were undertaken to investigate DMSO's potential therapeutic uses. Soon reports began to surface that the compound appeared to be a local analgesic and anti-inflammatory agent — and that it seemed to be effective in treating a wide range of conditions, including acute musculoskeletal injuries; diseases of connective tissues, such as gout and rheumatoid arthritis; viral, bacterial, fungal and parasitic infections of the skin; burns; postoperative pain; interstitial cystitis, an inflammation of the bladder; and the mental retardation associated with Down's syndrome.

But in 1965, the Food and Drug Administration learned that toxicity studies with experimental animals were showing links between both oral and dermal applications of DMSO and eye lens damage that ranged from mild myopia to cataract formation; the agency severely restricted the human trials of DMSO. However, in the years to follow, there would be a consistent lack of evidence of such eye damage in human trials, and the restrictions eventually were relaxed.

Now, about 35 human DMSO trials are underway. These include a study by Lawrence E. Pitts and colleagues of the University of California at San Francisco to determine whether intravenously administered DMSO is effective in reducing the elevated intracranial pressure associated with head injuries; a collection of studies supported by the National Institutes of Health to test whether DMSO is effective in treating the sores associated with a skin disease called scleroderma; and various studies to decide if the compound is useful in treating acute injuries such as sprains and strains. Definitive results from these studies are not expected for many months.

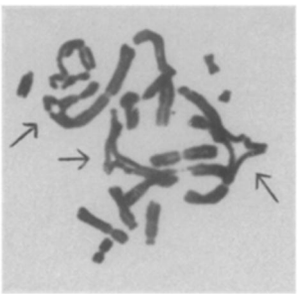
Meanwhile, DMSO use for the general public, outside of these controlled trial situations, has the FDA okay for only one illness — interstitial cystitis. For such cases, FDA has approved a 50 percent DMSO solution, marketed by Research Institute Corp. as Rimso-50, that is administered via a catheter. *This is the only DMSO product that thus far has received the FDA stamp of approval for human use.*

Nonetheless, an estimated 5 to 10 percent of the U.S. population is using stronger DMSO solutions to treat muscle strains, arthritis and the like. It is possible, for example, to obtain a 90 percent solution or gel that is labeled "For Veterinary Use Only" and is intended for use on horses and dogs to reduce acute swelling caused by injuries. In addition, the industrial solvent, which is about a 99 percent DMSO solution with unknown impurities, is sold over a variety of counters or by mail order to the general public. And, says Richard Crout of NIH, FDA is not likely to take any action against vendors of this latter product, as long as it contains no labels suggesting the compound be used for medicinal purposes. The agency would be on weak legal ground if it tried to halt sales of industrial-strength DMSO products that bear no such labels, Crout explains.

Finally, over the past several years, 10 state legislatures — those in Florida, Kansas, Louisiana, Minnesota, Montana, Nevada, Oklahoma, Oregon, Texas and Washington — have legalized the manufacture, prescription and use of DMSO in concentrations and applications other than the one approved by FDA. According to Oregon's law, the most liberal of the bunch, the DMSO need not even be manufactured within the state. In this situation, FDA can more easily build a case that could lead to the seizure of DMSO products: "We have informed the powers that be in Oregon that anything crossing state line is subject to the federal law, and we'll conduct ourselves accordingly," an FDA official explains.

That state legislatures are taking DMSO matters into their own hands is perhaps the most vivid illustration of a belief popular among the chemical's proponents — that FDA has purposely dawdled away its hours on the DMSO issue. "The DMSO story has no counterpart," says the chemical's leading proponent, Stanley Jacob of Oregon Health Sciences University in Portland; "there has been no other drug that has been treated with less fairness and objectivity by FDA."

(Jacob, the principal discoverer of



Patterson

*Arrows mark chromosomal aberrations in DMSO-treated cells.*

DMSO as a potential therapeutic agent for human illnesses, is himself somewhat of a controversial figure in the DMSO story. In October, he went on trial in federal court, charged with a "gratuity offense"—paying $36,500 to a then-FDA official who was evaluating DMSO for the agency. Jacob, a surgeon, claims that part of the money was a contribution to a medical foundation in the official's native India and that the rest was a loan to help the official pay the medical bills of his wife, who died from diabetes in 1977. "There is a far cry between imprudence and a felony, with which I was charged," Jacob told SCIENCE NEWS. On Oct. 29, the charges against him were dismissed after he admitted before the court that what he had done was improper. Meanwhile, the former FDA official, K.C. Pani, pleaded guilty to a misdemeanor charge of receiving an outside supplement to his government salary for official services. On Dec. 6, he was sentenced to one year of unsupervised probation and 200 hours of community service.)

Jacob says that the DMSO issue has dragged on for decades in part because pharmaceutical companies probably would not be able to secure strong patents that involve only the chemical. "It's not patentable by ordinary techniques, because it was a known chemical for years before its medicinal uses were discovered," Jacob explains. Pharmaceutical companies could try patenting it for specific medicinal uses, but such patents are easily challenged, he says. As a result, "there is no great enthusiasm on the part of pharmaceutical companies and so less enthusiasm on the part of FDA" to approve more human uses for DMSO, says Jacob.

But at the recent New York Academy of Sciences "Conference on Biological Actions and Medical Applications of Dimethyl Sulfoxide," FDA's John Harter said that such an idea "is ludicrous to anyone knowledgeable about the FDA, the medical-scientific community and the pharmaceutical industry, even when it is cast in its most sinister role with profit as its mainspring." The FDA will be "willing, indeed anxious" to approve DMSO for new applications, said Harter, when "adequate and well-controlled" trials yield data that support such approvals.

Harter explained that many of the previous clinical trials with DMSO were scientifically inadequate partly because the study designs failed to control for subject expectations due to the obvious difference between placebos and DMSO. The most noticeable reactions to DMSO are itching and redness over the skin and a garliclike taste and odor on the breath that occurs within minutes of administration. "Some investigators attempted to make placebos by using substances like histamine [to cause the skin reactions] and garlic," Harter said, but they "were unsuccessful . . . in fooling patients who had had previous experience with DMSO."

FDA now recommends that investigators design studies that involve comparing the effects of different doses of DMSO, rather than the effects of placebos versus DMSO, in order to minimize the bias that has plagued previous human trials. In such studies, Harter reported, investigators need "to find two doses far enough apart on the efficacy-response scale to be distinguishable from one another statistically and yet close enough to each other on the side-effect scale."

Harter went on to say that another reason FDA has not yet approved DMSO for the general public other than for interstitial cystitis cases is that the agency has not forgotten the earlier incidence of eye damage in animals. Despite its subsequent relaxation of clinical trial restrictions, the FDA is reluctant to approve new widespread applications of DMSO until the matter is further investigated. "Our toxicologists have reviewed studies on DMSO in seven species, all of which, after some dose for some duration, show incompletely reversible changes in the lens," Harter reported; "it would be a biological quirk for human lenses not to behave similarly."

Rosalyn M. Patterson of Atlanta University in Georgia also believes more extensive, long-term investigations of the potential adverse side-effects of DMSO should be conducted. In research that has been submitted to MUTATION RESEARCH for publication, Patterson found an increased incidence of damage to chromosome (DNA-containing) material in DMSO-treated Chinese hamster ovary cell cultures. While only about 5 percent of the chromosomal material was found to be damaged in control cultures, up to 27 percent chromosomal aberration—including separations and gaps in the component chromatids — was found in cell cultures exposed to solutions of 1 to 4 percent DMSO. Although such cell culture chromosome damage by itself is not "a major concern," Patterson points out that in previous studies, congenital defects have been produced in chick embryos, rats, mice and hamsters by high doses of DMSO.

But meeting participant Jack de la Torre of Northwestern University Medical School in Chicago told SCIENCE NEWS, "There is no drug on the face of this earth that doesn't have toxic side effects given a large enough dose of the drug and a large enough population. . . . You have to weigh the disorder by what the drug is going to accomplish." And, says de la Torre, "I definitely think DMSO has a place in therapy for a number of serious disorders."

One such disorder, he says, may be the type of stroke caused by clots in the blood vessels of the brain — an affliction that strikes about 395,000 persons each year. De la Torre says there is a growing body of animal and laboratory evidence that DMSO not only can reduce swelling and inflammation, but also can deaggregate clotting vessel platelets and dilate (expand) blood vessels. In addition, the compound has been shown to cross the blood-brain barrier — the brain's protective barrier of tightly joined fatty cells that form the blood-carrying capillaries to the brain and that keeps out unwanted toxic substances but also prevents some useful therapeutic agents from entering. (DMSO's ability to penetrate the blood-brain barrier of mice and to "open" it to a chemical that normally cannot break through that blockade was reported by Richard D. Broadwell and colleagues of the University of Maryland School of Medicine in Baltimore in the July 9 SCIENCE.) And now, says de la Torre, there is evidence that these reported abilities may be beneficial in arresting or reversing the brain ischemia (deficit in oxygen-carrying blood matter) that follows a stroke.

De la Torre and colleagues have simulated stroke-induced brain ischemia by tying off the middle cerebral artery in rhesus monkeys. Five of the 10 monkeys used in the experiment intravenously received 2.5 grams of DMSO per kilogram of body weight four hours after the artery was tied. The artery was re-opened after about 16 hours, and the monkeys were killed seven days later. De la Torre and cohorts then examined the animals' brains and found significantly less swelling and tissue injury in the DMSO-treated monkeys than in the untreated ones.

"When the delivery of oxygen and nutrients to the tissue is deficient or nonavailable, as in ischemia, cell damage or death, with all its attending pathological consequences, becomes an end-point," de la Torre reported. "We conclude ... that DMSO is able to intervene at various levels of this [process]."

But John R. Little of the Cleveland Clinic Foundation in Ohio says that no such conclusion of beneficial effects can be drawn from an experiment that uses so few animals. And besides, it is questionable whether any beneficial effect actually can be observed in a situation that involves administering the presumed therapeutic agent four hours after the traumatic artery-clipping event: "De la Torre didn't even give DMSO until a time others would consider irreversible damage to have occurred using this model," Little explains.

Little and colleagues used the same middle-cerebral-artery-clipping model to

*Continued on page 408*

**Continued from page 399**

induce brain ischemia in 20 cats and 15 baboons. However, in their study, the DMSO-treated cats began receiving the compound immediately after the artery was closed, and the DMSO-treated baboons began receiving the chemical 30 minutes after artery clipping. Despite this swift administration of the compound, Little and cohorts found no significant physical differences between treated and untreated animal brains. "The findings of our investigation indicate that DMSO is ineffective in treating . . . brain ischemia," Little reported at the recent DMSO conference. Later, he told SCIENCE NEWS, "It would be a waste of time to continue [such DMSO-brain ischemia] studies."

However, Little added, while he does not share de la Torre's enthusiasm in pursuing the possibility of DMSO therapy for stroke victims, he does believe other avenues of DMSO research are worth pursuing. For example, at the conference several groups presented results of animal studies that suggest DMSO may prove useful in alleviating the intracranial pressure caused by brain injuries that are generally less serious than strokes (such as blows to the head).

Also, the results presented in a late-arriving, unannounced paper by Spotswood Spruance of the University of Utah at Salt Lake City were deemed encouraging by other meeting participants. Spruance and colleagues injected herpes viruses into the backs of guinea pigs. They then tested whether the effectiveness of acyclovir in treating herpes lesions increases when DMSO is added to the drug. (Acyclovir is a Burroughs-Wellcome Co. ointment that last spring met with FDA approval for treating initial infections of genital herpes [SN:4/10/82, p. 247].) Spruance found that topically applied doses of acyclovir that were not combined with DMSO reduced herpes lesions by only 18 percent; doses combined with DMSO, on the other hand, reduced lesions by 80 percent.

"If this is corroborated," says de la Torre, "I think it's going to be quite an interesting story." It suggests not only that DMSO can significantly enhance penetration of the herpes-fighting acyclovir, but also that the effectiveness of other topically applied therapeutic agents could be enhanced in a similar fashion, he says.

But Patterson says it is these carrier and penetrating abilities of DMSO that may pose a greater threat to patients than the chemical itself. Topically applied DMSO could carry environmental chemicals — such as toxic substances that are used in a workplace setting — into the body, she explains.

Nonetheless, says Jacob, the DMSO-acyclovir duo is the type of DMSO product for which a strong patent could be secured. And he predicts, "This is . . . the sort of thing you're going to see [approved by FDA and on the market] next." □