Can Drugs Ever Be Safe?

The benefit of any drug must be weighed against its "calculated risk," for not everyone is equally safe from reactions—By Faye Marley

➤ RECALL of the "wonder drug" DMSO, short for dimethyl sulfoxide, from experimental use by physicians on their patients is an example of the extreme caution of the U.S. Food and Drug Administration.

The decision to end clinical testing was based on evidence that the drug impairs the sight of laboratory animals. After careful consideration of its benefits in some disease conditions, however, doctors may prevail upon the FDA to lift the ban.

A mid-March meeting on the biological actions of DMSO, sponsored by the New York Academy of Sciences, brought together representatives from FDA and the American Medical Association, and clinical and laboratory investigators from universities, drug companies and further research institutions.

DMSO was reported to be useful by research scientists and doctors. It can soften and reduce in size the thick, hard tissue that forms under the skin following intensive radiation treatment for cancer. The drug, coupled with physical therapy, relieved an arthritic condition called frozen shoulder, unrelated to rheumatoid arthritis, making both injections into the shoulder and pain-killing narcotics unnecessary.

Are these benefits sufficient to risk side effects?

New Procedures Inaugurated

The U.S. Food and Drug Administration under its new Commissioner, Dr. James L. Goddard, is inaugurating new reporting procedures intended to streamline the reviewing of reports from pharmaceutical companies. Reports on DMSO alone weighed about a ton and qualified personnel have been hard to find.

A longer waiting period after experiments with animals to evaluate results before FDA authorizes testing of drugs on humans has been proposed by a North Carolina Congressman. Subcommittee Chairman L. H. Fountain (D.-N.C.) made the proposal at a hearing of the Subcommittee on Intergovernmental Relations to the House Committee on Government Operations in March.

Commissioner Goddard is considering this proposal, he said. He explained FDA controls over the interstate distribution and use of investigational new drugs at the hearing of the Fountain committee where accusations were heard both against drug companies and FDA officials.

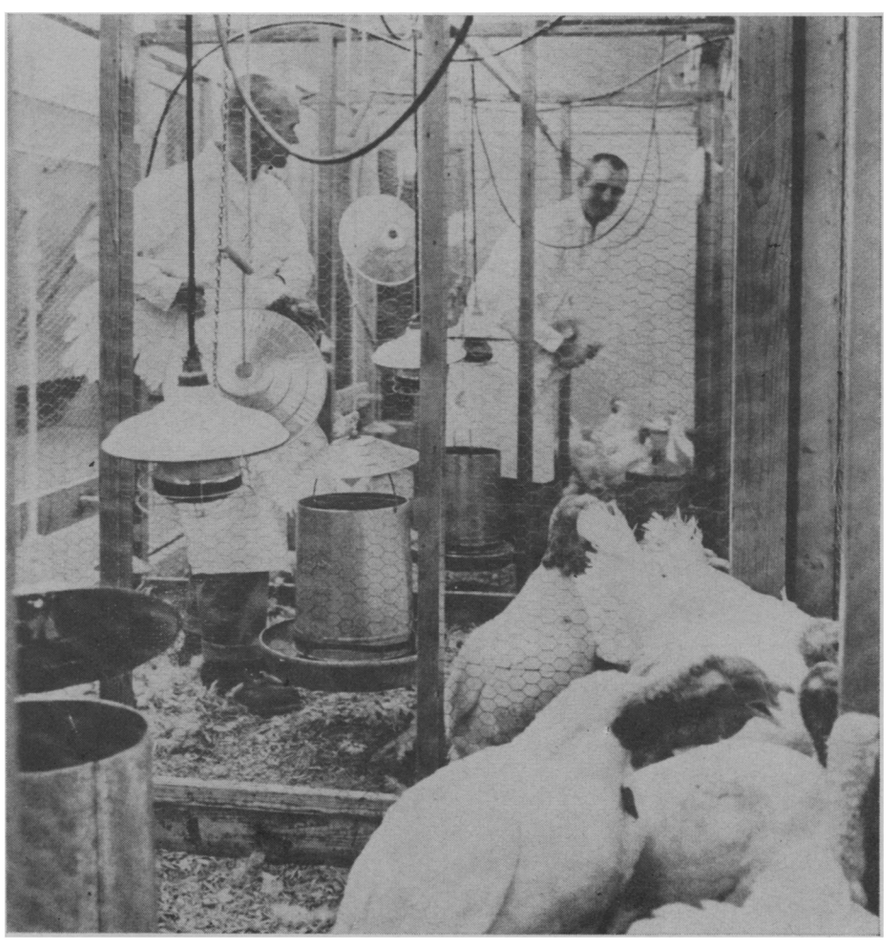
Even before the Kefauver-Harris Drug Amendments were enacted in October 1962, Secretary Anthony J. Celebrezze of the Department of Health, Education and Welfare had announced the proposed tightening of controls over investigational new drugs. Congress endorsed the step.

It was in January 1963 after FDA had received and studied written and oral comments from virtually the entire scientific community and the pharmaceutical industry, that the regulations were issued in final form.

They require that the sponsor of any investigational new drug must first present to the FDA an acceptable plan for the investigation.

The plan must describe in adequate detail what the drug is, how and where it is made and how it is controlled to meet appropriate standards of strength, quality and purity. In this way only, can significance be given to the investigations. A statement must be made to show what is known about the drug from experience with humans in other countries or from clinical experience with related drugs. The sponsor must state exactly what information is to be sent out to investigators who are to use the drug. The scientific training of the investigators must be known as well as other necessary information.

Basic studies with laboratory animals must be reported in adequate detail so that scientific evaluation can be made. The preclinical investigations will not be considered "adequate"



Ciba

HUMAN DRUG HELPS TURKEYS—A tranquilizer that is effective in humans has been added to the food of animals. These turkeys are receiving Serpasil Premix at the Ciba agricultural-veterinary farm to prevent or control outbreaks of aortic rupture.

to justify testing on humans unless they give proper attention to the conditions of the proposed clinical testing.

"This means that if long-term use of the drug in clinical test is contemplated, there must be long-term animal studies to justify it," said Dr. Goddard.

Phases one and two deal with human pharmacology. Phase one is the investigation with volunteers, covering human toxicity, metabolism, absorption, excretion and dose range. Phase two covers the initial trials on a limited number of patients for prophylaxis of a specific disease.

Clinical Trial

Phase three is the clinical trial. The animal experimentation needed to assess the safety of these investigations must be completed before this all-important phase is undertaken.

Records must be maintained, and if there is any adverse experience, the sponsor is required to report it promptly.

An alarming finding in animal tests can be cause to discontinue the investigation, and the same is true for any evidence that shows a substantial doubt as to safety of the drug for man. The drug itself must be labeled as an investigational drug.

FDA has the right to order discontinuance of an investigational plan in whole or in part, if it contains false data, if the results show it is not reasonably safe to continue, and if these other "ifs" exist:

If the plan is not being followed, the drug is shown to be unsafe or ineffective, the manufacturing facilities and controls are inadequate, the plan is not a reasonable one, the drug is improperly commercialized, if the data supplied to the investigators does not provide full information about hazards. If records are not kept, if progress reports are not made, or if the sponsor fails to investigate and report adverse experience gained during the clinical trial.

Investigators Will Protect Public

The FDA's plan to use Georgetown University Medical School's faculty and facilities in review of basic medical issues through a clinical pharmacological laboratory in that school will be expanded to other schools. This will strengthen FDA and provide scientific investigators to protect the public from mistakes.

"We have a delicate problem in investigating the investigator," admitted Dr. Goddard. "Scientific personnel are not accustomed to being questioned by regulatory agencies. But some investigations will have to be made, and when it becomes necessary to do so, every effort will be made to minimize misunderstanding."

SCIENCE SERVICE has previously reported on the failures to meet regulation requirements on DMSO.

"DMSO was an exciting drug to the public and to the profession because of its unique absorption," said Dr. Goddard. "Its extravagant promotion led to its use by persons not at all authorized to have it." Indeed, the demand was so great that the industrial grade of this by-product of the paper industry was used by some thoughtless physicians.

Other crackdowns by the FDA on first one drug and then another—most recently a whole series of antibiotic lozenges—has aroused the public as well as drug manufacturers. Can a drug ever be entirely safe? Probably not, experts say. Even aspirin is going to give trouble to some stomachs. But long, patient testing will show reasonable safety if patients are watched carefully by doctors.

As an appalling example, the use of thalidomide in Germany and other countries has left deformed children to grow up after a fashion with prosthetic limbs to testify to the mistake their mothers made in using the drug during early pregnancy. Thalidomide was the wrong choice of sedative, although it was safe enough on nonpregnant women and animals. Some pregnant women took it and had normal babies. The study goes on—when did the deformity occur in pregnancy, and why?

Prominent pharmacologists are fearful that the birth control pills now being taken by millions of women can prove to be a mistake in the coming generation. It is too soon to know. Because one woman gets cancer or jaundice or experiences some other side effect traced to the pills, should all women give them up?

What human being wants to be a guinea pig? None. This is the reason that monkeys and lower animals are logical stand-ins for humans. Their suffering and death under humane circumstances are justifiable to make drugs safer, the world of science affirms.

PHARMACOLOGY

Drug Appraisal Asked

➤ A "FAIR and balanced appraisal" of the substantial achievements of the drug industry in developing medicines to treat disease and prolong life was asked by a physician who is also head of a leading drug manufacturing company.

Dr. J. Mark Hiebert, board chairman of Sterling Drug Inc., said at a Pharmacy Colloquium in Lawrence, Kans., held in conjunction with the University of Kansas' Centennial Observance, that more than one billion prescriptions will be filled in the pharmacies of the United States this year, of which almost 95% will be produced in their entirety by pharmaceutical manufacturers.

"This huge number of prescriptions," he said, "symbolizes the responsibility of the manufacturer in his task of producing efficacious medicines of high quality and safety, and this is uppermost in the manufacturer's mind."

Dr. Hiebert, a member of the Council for Progress of the University of Kansas, stated:

1. There is always room for improvement—in the pharmaceutical industry and everywhere else. Criticism can be most helpful in guiding such improvement, "but I think we have a right to responsible perspective in the evaluation of our industry's achievements."

2. The pharmaceutical industry of today is quite different from that of a generation ago. "Modern drugs are highly potent. They can be, and often are, lifesaving; but, by comparison with the medicaments of yesteryear, the margin between therapeutic dose and toxic dose is substantially narrowed. In the discharge of his responsibilities, the manufacturer of pharmaceutical products must never forget this."

3. The total responsibility for the health of our population is shared by many. "In the exercise of this responsibility by all who share it, distrust must give way to faith, suspicion to confidence, prejudice to objectivity."

4. There is risk in every type of product, in life itself. "It is urgent that risk be minimized to the greatest extent possible; but it is no more possible to attain zero risk than to find the end of infinity. Safety consists in the judicious balancing of benefits and risk."

5. Safety has other dimensions of critical importance. "Safety requires the courage to say 'yes' to a new drug as well as the judgment to say 'no.' The 'yes' answer is urgent when it can mean safety from imminent probable death."

6. Individual safety is also the responsibility of the individual. "There is no known way of eliminating personal carelessness by legislation." Medicaments on the market are acceptably safe when used as directed on the label or by the physician. Danger develops in one's own home when useful products—medicines, kerosene, powerful detergents, insecticides, whiskey, even common salt—are misused or abused.

Dr. Hiebert further stated that obligations were to create through research more and more life-saving and health-preserving medicines; bring to the attention of physicians all new developments that may favorably affect the health of their patients; and notify the medical profession immediately if product error occurs, and if safety is at stake, withdraw the product at once.

"If the pharmaceutical manufacturer is not to be overburdened by statutes and regulation," Dr. Hiebert said, "he must practice self-discipline."