Meetings

Toxicology: Use of Nonhuman Primates

The Food and Drug Administration (FDA) has statutory responsibility for the safe use of drugs, food additives, and hazardous substances distributed in interstate commerce. The initial use in man of a chemical compound having drug potential may possibly cause toxicity hazards. While it is common practice to attempt to predict human toxicity of such compounds from toxicity data obtained in several species of lower mammals, extrapolation of such data may not always be predictive. A biological model of man is needed to predict toxicity of chemical compounds in man. Because in many respects nonhuman primates resemble man more closely than do lower animals, a combination of these animals might be used as a composite primate toxicity model for man.

To this end, FDA sponsored a Conference on Nonhuman Primate Toxicology at Airlie House, Warrenton, Virginia, 12–14 June 1966. Approximately 60 percent of the 60 participants were from academic institutions and industrial research laboratories; 40 percent were from the National Institutes of Health and FDA. Leon H. Schmidt (director, National Center for Primate Biology, Davis, California) was general chairman of the Conference. William H. Summerson (FDA Bureau of Science) welcomed the participants on behalf of the Commissioner of Food and Drugs and expressed FDA's need for new approaches to toxicological problems.

Harry F. Dowling (University of Illinois College of Medicine) gave the opening address on "Why research on the subhuman primates?" He outlined man's progress in reducing the risk to human life in testing and evaluating potential healing agents by using animals wherever possible. With increasing availability of nonhuman primates and because of their phylogenetic relationship to man, their use in drug experimentation and evaluation is increasing.

Schmidt discussed the problems of management of a nonhuman primate colony for toxicological evaluations, based on his 30 years of experience. Good pharmacological and toxicological data can be obtained only from well-managed, healthy colonies. He discussed the problems of procuring and conditioning the animals before they are introduced into the colony, parasitic examination and treatment of new arrivals, caging and restraining techniques, continual day and night vigilance for appearance of malaise and first symptoms of infection, and qualifications of caretakers.

The qualitative and quantitative relationship between toxicity of drugs in man, lower mammals, and *M. mulatta* were compared by Frederick Coulston (Albany Medical College of Union University). He considered several routes of administration, histological effects, and metabolic disposition. The tabulated toxicity data on 20 drugs and chemicals did not reveal that any one laboratory animal, including *M. mulatta*, is a more satisfactory predictor of toxicity than the others, although each resembled man in certain respects.

To answer the question, "Do studies of drugs in subhuman primates predict metabolic disposition in man better than parallel studies in other laboratory animals such as the dog," Carl G. Smith (Christ Hospital of Medical Research, Cincinnati) had collected data on the metabolism of 11 drugs in man, dog, and the monkey. Comparison indicates that neither the monkey nor dog represents an ideal model animal for predicting the metabolic fate of a drug in man. As yet it is impossible to decide from these data whether one of the other subhuman primates might represent a significantly better model than the rhesus monkey on which most of the studies have been conducted. For most compounds the chances of predicting the metabolic fate in man would be better based on metabolism data from rhesus monkeys than from dogs. There is considerable room for improvement in predictability, suggesting the need for systematic drug metabolism studies in a larger sample of subhuman primates.

Maurice H. Seevers (University of Michigan) has been studying the problem of drug addiction for more than 40 years, using *M. mulatta* as the test subject. He has developed an accepted screening technique for drugs having unknown addicting potential. Monkeys addicted to morphine are withdrawn from the medication for 14 hours. By this time profound withdrawal symptoms have appeared. The drug to be tested is then given to the monkey. If the withdrawal symptoms are relieved, the test drug is considered addictive.

Herbert H. Reynolds (Holloman Air Force Base) discussed assessment of toxicological effects on the central nervous system at the Aeromedical Research Laboratory. Chimpanzees and macaque monkeys are being used to study toxic hazards to which man may be exposed in space and space-related operations.

Nonhuman primates have also been used in studies of reproductive activities. Gertrude Van Wagenen (Yale University) summarized her 30 years of studies on fertility, and James G. Wilson (University of Florida) summarized the results of teratogenic studies in the nonhuman primates. Van Wagenen explained that the events in the reproductive period of the female *M. mulatta* closely resemble those of woman. They experience a menarche, a fertile period, and menopause. Her studies have included the effects of various hormones on sexual development. Wilson summarized the published literature on teratogenesis in the nonhuman primate, reported on his personal studies, and reported a survey of all known laboratories who had controlled programs of primate breeding. Before one can evaluate the findings of experiments on induced teratogenicity, a base line for the incidence of spontaneous malformations must be established. In an attempt to get this data, Wilson designed a questionnaire to which he received 40 replies. All malformations noted in the monkey or ape could be readily duplicated in human teratology.

The three substances known to be teratogenic in man—thalidomide, rubella virus, and steroids with androgenic activity—are also teratogenic in primates (two species). Wilson reported in more detail his studies of thalidomide in *M. mulatta*.

Samuel Saslaw (Ohio State University) feels the nonhuman primates can

be useful in evaluating hematotoxicity. Over the past 25 years he has studied the hematological responses of rhesus and cynomolgus monkeys to infections, toxic and irradiating agents, and nutritional deficiences. He has shown that primates exhibit marked similarities to those observed in man. He believes that these primates offer unusual opportunities for such studies in depth.

Species differences, with regard both to the manifestations of hypersensitivity and to drug metabolism, make it difficult to find an adequate test model for studies of drug-induced hypersensitivity in man. Arthur Malley (Oregon Regional Primate Research Center) discussed skin manifestations of drug toxicity in nonhuman primates.

W. C. Stebbins (University of Michigan Medical School) described the method which he is using for evaluating the effects of ototoxic drugs on hearing in monkeys; behavioral audiometry is followed by micro-dissection of the cochlea and phase-contrast microscopy of longitudinal preparations of Corti's organ.

Small bowel ulceration occurred in humans after they had taken orally enteric-coated, potassium chloride tablets or thiazides with enteric-coated potassium chloride tablets. Such reactions prompted Robert M. Diener (Ciba Pharmaceutical Products) to investigate the enteric effect of enteric-coated, potassium chloride in the dog, the rat, and the monkey. Administration of these drugs to dogs produced only mild lesions which did not resemble those observed in man and did not produce lesions in rats. However, rhesus monkeys who were given the approximate human dose experienced intestinal ulceration similar to that noted in man.

While nonhuman primates have been used in the experiments involving the administering of a variety of aerosols, Norton Nelson (New York University Medical School) stated that the investigations have not been extensive, or always thorough. He discussed the physical principles involved and the histological effects.

Many other scientists with research experience with nonhuman primates participated in the discussion of the summary papers. The proceedings of the conference will be published and will be available for purchase.

CLEM O. MILLER
Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C. 20204

Calendar of Events

National Meetings

July

9–13. American **Veterinary** Medical Assoc., 104th annual mtg., Dallas, Tex. (Executive Secretary, 600 S. Michigan Ave., Chicago, Ill. 60605)

10–11. American College of **Laboratory Animal Medicine**, annual mgt., Dallas, Tex. (R. H. Yager, Secretary, ILAR-NRC, 2101 Constitution Ave., NW, Washington, D.C. 20418)

10–12. **Aviation and Space Transportation,** symp., New York, N.Y. (American Soc. of Mechanical Engineers, 345 E. 47 St., New York 10017)

10–14. Nuclear and Space **Radiation Effects**, Columbus, Ohio. (IEEE, Technical Activities Board, 345 E. 47 St., New York 10017)

14–15. Rocky Mountain **Cancer** Conf., 21st, Denver, Colo. (N. P. Isbell, Colorado Medical Soc., 1809 E. 18 Ave., Denver 80218)

17–19. Sixth **Aerospace Reliability and Maintainability** Meeting, Cocoa Beach, Fla. (Meetings Manager, ASME, 345 E. 47 St., New York 10017)

17–21. **Neutron Thermalization and Reactor Spectra**, Ann Arbor, Mich. (J. H. Kane, Intern. Conf. Branch, Technical Information Div., Atomic Energy Commission, Washington, D.C.)

17–21. Third **Propulsion** Joint Specialist Conf., Washington, D.C. (Meetings Dept., American Inst. of Aeronautics and Astronautics, 1290 Sixth Ave., New York 10019)

18–20. **Electromagnetic Compatibility**, 9th symp., Washington, D.C. (F. T. Mitchell, Atlantic Research Corp., Shirley Hwy. and Edsall Rd., Alexandria, Va.)

18–22. American **Medical Technologists**, 29th annual mtg., Washington, D.C. (C. B. Dziekonski, 710 Higgins Rd., Park Ridge, Ill. 60068)

19–21. **Marine Chemists** Assoc., 9th annual mtg., San Francisco, Calif. (K. M. Savage, c/o National Fire Protection Assoc., 60 Batterymarch St., Boston, Mass.)

24–27. American Soc. for **Metals**, W. H. Eisenman Conf. on Metal Ceramics Composites, San Francisco, Calif. (The Society, Metals Park, Ohio 44073)

24–28. Solid **Waste** Research and Development, conf., Milwaukee, Wis. (United Engineering Center, 345 E. 47 St., New York 10017)

24–29. **Fluorine Chemistry**, 4th intern. symp., Estes Park, Colo. (P. Tarrant, Dept. of Chemistry, Univ. of Florida, Gainesville 32601)

27–29. **Linguistic** Soc. of America, annual summer mtg., Ann Arbor, Mich. (A. A. Hill, Box 8120, University Station, Austin, Tex. 78712)

30–3. American Soc. of **Animal Science**, mtg., Reno, Nev. (A. M. Pearson, Dept. of Food Science, Michigan State Univ., East Lansing 48823)

31–2. International Soc. for Human and Animal **Mycology**, 4th conf., New Orleans, La. (R. Baker, Louisiana Univ. School of Medicine, New Orleans)

31–4. **Mammalian Oviduct**, symp., Pullman, Wash. (E. S. E. Hafez, Reproduction Lab., Washington State Univ., Pullman 99163)

31–4. Association for the Advancement of **Medical Instrumentation**, annual mtg., San Francisco, Calif. (J. J. Post, Box 314, Harvard Sq., Cambridge, Mass. 02138)

31–4. **Particulate Matter** Systems, conf., Milwaukee, Wis. (United Engineering Center, 345 E. 47 St., New York 10017)

International and Foreign Meetings

July

9–15. American Soc. for **Horticultural Science**, Tropical Region, 15th annual mtg., Panama. (E. H. Casseres, Calle Londres 40, Mexico 6, D.F., Mexico)

10–12. Naturally Occurring **Phosphoric Esters**, intern. symp. Newcastle-upon-Tyne, England. (General Secretary, Chemical Soc., Burlington House, London, W.1, England)

10–15. International **Mining** Congr., 5th, Moscow, U.S.S.R. (A. S. Archangelsky, c/o Ministry of the Coal Industry of the U.S.S.R., B. Kiselny per., 13/15, Moscow K-45)

10–15. Latin American **Soil Biology**, 2nd congr., Santa Maria, Brazil. (Science Dept., British Council, Albion House, 59 New Oxford St., London, W.C.1, England)

11–14. **Magnet Technology**, 2nd intern. conf., Oxford, England. (R. C. Pepperell, Rutherford High Energy Laboratory, Chilton, Didcot, Berkshire, England)

11–14. International Union of **School and University Health Medicine**, 5th congr., Prague, Czechoslovakia. (The Union, Centre International de l'Enfance, Château de Longchamp, Bois de Boulogne, Paris 16e, France)

12–14. International Soc. for **Clinical and Experimental Hypnosis**, 5th congr., Kyoto, Japan. (Y. Ikemi, c/o Dept. of Psychosomatic Medicine, Kyushu Univ., School of Medicine, Fukuoka City, Japan)

14–28. **Plant Pathology**, 1st intern. congr., London, England. (R. K. S. Wood, Imperial College, London, S.W.1)

15–18. **Electrical Contact Phenomena**, intern. research symp., Swansea, Wales. (Meetings Officer, Inst. of Physics and the Physical Soc., 47 Belgrave Sq., London, S.W.1, England)

16–22. Organic **Photochemistry**, intern. symp. (IUPAC), Enschede, Netherlands. (W. G. Dauben, c/o Dept. of Chemistry, Univ. of California, Berkeley 94720)

17–19. **Organic Chemistry**, symp., (IUPAC), Nottingham, England. (A. W. Johnson, Dept. of Chemistry, Univ. of Nottingham, Nottingham)

17–21. **Solar-Terrestrial Relationships** during Solar Minimum Conditions, symp., London, England. (G. de Q. Robin, c/o Scott Polar Research Inst., Univ. of Cambridge, Cambridge, England)

17–22. World **Veterinary** Assoc., 18th intern. congr., Paris, France. (R. Vuillaume, 27, rue des Petits-Hôtels, Paris 10e)

18–23. **Laser Applications**, 1st intern. congr., Paris, France. (The Congress, 14, rue de Buffon, Paris 5e)

19–22. Ibero-Latin American Congr. of **Dermatology**, Barcelona, Spain. (J. Pinol-Aguade, c/o Facultad de Medicina, Univ. de Barcelona, Spain)