Meetings

Pharmacology-Toxicology

The effects of age, stress, drugs, disease, sex, season, and heredity on the metabolism, safety, and effectiveness of drugs was the subject of a symposium sponsored by the National Institute of General Medical Sciences at Gaithersburg, Maryland, 8–10 May 1969.

Human variability factors help to explain differences in the responsiveness of individual patients to drugs. The use of such factors in predicting either the desirable or the deleterious effects of drugs was examined.

C. Mitoma provided evidence that an individual who metabolizes one drug slowly may also metabolize other drugs slowly. His investigations also showed that animals exposed to a drug during the perinatal period tolerated the drug better than did newborn animals who were not previously exposed.

S. Fabro described experiments in which the lipid solubility, degree of ionization, and molecular weight seem to be important factors which correlate well with the penetration of drugs into the preimplantation blastocyst.

W. F. Bousquet demonstrated that histamine caused a drop in the blood pressure of the rat during the period from September to January, whereas larger doses failed to alter the blood pressure during the period from May to August. These seasonal or circannual rhythms exhibit a peak-and-trough relationship between summer and winter months.

Alpha-methyltyrosine depleted brain norepinephrine (NE) more than 80 percent in animals subjected to environmental stressors. Brain NE in the nonstressed animals was depleted only 45 percent. Slight structural modification of this drug to alpha-methylparatyrosine prevented the stress-induced elevation in blood pressure and actually lowered it in animals exposed to chronic stress, according to J. P. Buckley.

J. L. McNay presented evidence that hepatic blood flow is a significant factor in determining the rate of hepatic metabolism of oxyphenbutazone.

F. F. G. Sjöqvist reported that the same total dose of desmethylimipramine (DMI) or nortriptyline (NT) in patients with various forms of depression yielded steady-state plasma levels which varied 10- to 30-fold. However, the steady-state plasma level was reproducible and proportional to dosage in the same patient. He concluded that the steady-state plasma level of NT is controlled by both genetic and environmental factors. The steady-state plasma level is also largely determined by the rate at which NT is metabolized. Crossover experiments indicate that patients who develop low or high steady-state levels of DMI also develop similar levels of NT.

S. Garattini told of experiments with diazepam which rapidly accumulates in the brain at a rate depending, among other factors, upon storage in adipose tissue and metabolism in the liver. This drug is metabolized by hepatic microsomal enzymes to form *N*-demethylated and C-3-hydroxylated products. The three major metabolites of diazepam, namely, *N*-methyloxazepam, *N*-demethyldiazepam, and oxazepam, are active metabolites. *N*-Demethyldiazepam accumulates in plasma of humans after repeated use of diazepam.

M. Rowland discussed a study of lidocaine, which is employed in the control of cardiac arrhythmias. Patients in heart failure were found to exhibit a decreased volume constant and total body clearance which together result in elevated plasma levels on the normal dosage regimen. He suggested that these changes constitute a principal cause of toxic reaction observed in some patients receiving accepted clinical doses of this drug.

Phenobarbital produces its inductive effect by increasing the synthesis of a hemoprotein with two different binding sites, according to G. J. Mannering. However, the polycyclic hydrocarbons cause the synthesis of an aberrant hemoprotein possessing only one of the two binding sites.

Studies on the isolation of hemoprotein showed that, by appropriate adjustment of ionic strength, one could cause the preparation to form microtubules. Binding occurred only when the tubular elements were present, and cytochrome P-420 appears to be an integral part of the tubule or very closely associated with it.

J. R. Fouts reported that drugs and hepatotoxins which affect different parts of the endoplasmic reticulum (ER) will have different effects on microsomal drug metabolism if the drug-metabolizing enzymes are not distributed evenly through the ER. Animal species seem to differ in the localization of these enzymes in the subfractions of the microsomes and in response of these subfractions to chemicals which are enzyme inducers or hepatotoxins.

The evidence indicates that TPNH and P-450–requiring enzyme activities are relatively concentrated in smooth ER, while glucuronyl transferase activities are found concentrated in rough-surfaced ER or evenly distributed throughout both types of ER. Enzyme inducers do affect enzyme activity distributions between microsomal subfractions, with phenobarbital being at one extreme (increased proportions of enzyme activity in smooth ER) and 3-methylcholanthrene at the other (increased proportions of enzyme activity in rough ER).

M. Rowland presented an analysis of griseofulvin plasma levels and urinary excretion of its metabolites, with and without concomitant phenobarbital administration. His data show that, rather than stimulating the enzyme responsible for its metabolism, phenobarbital depressed the absorption of griseofulvin.

Patients given methylphenidate and imipramine in combination showed clinical improvement and an increase in the sum of the plasma concentration of imipramine and desmethylimipramine, in studies discussed by P. G. Dayton.

Therapeutic doses of methylphenidate, given for the minimal cerebral dysfunction syndrome, were found to raise the serum levels of primidone, diphenylhydantoin, and phenobarbital in a child. Methylphenidate also slowed the rate of disappearance of ethyl biscoumacetate from serum.

A. H. Conney reported that cigarette smoking markedly increases the activity of enzymes in human placenta which hydroxylate the 3,4-benzpyrene and which *N*-demethylate the 3-methyl-4-monomethylaminoazobenzene commonly found in smoke. No detectable benzpyrene hydroxylase or aminoazo dye *N*-demethylase activity was ob-

served in human placentas from nonsmokers after normal childbirth. However, these enzymes were found in placentas obtained from smokers.

K. H. Palmer described the metabolism of norethindrone which, in sharp contrast to norethynodrel, was metabolized only to a limited extent. The metabolites of norethynodrel in animals and man were identified and their structures confirmed by unequivocal synthesis.

M. S. Fahim and D. G. Hall suggested that progesterone affects the livers of sexually mature female rats in a manner similar to phenobarbital, causing increased liver weight, hepatic demethylation, hepatic microsomal protein, and excretion of ascorbic acid in the urine. Although progesterone appears to function as an enzyme inducer in adult female rats, a reverse effect is noted in males.

Using the techniques of gas chromatography and an elegant combined technique employing gas chromatography–mass spectroscopy with an online computer, M. M. Horning and R. Hill provided a method for following the excretion of drugs and drug metabolites and the effect of drugs on normal metabolic pathways. These procedures provide permanent records which can be reexamined as additional information is accumulated.

From spatial considerations of molecular models of the drugs studied, P. Talalay and E. Bueding have defined with some precision the conformation of the drug at the active site of the enzymes. They provided evidence that structural analogies between chemicals need to be refined to also include careful consideration of configurational and electronic properties of molecules.

D. J. Holbrook described experiments on the interaction of a drug with nucleic acids which suggest plausible sites for the mechanism of action of a given drug. The binding of chloroquine and 8-aminoquinolines to DNA, RNA, and various polynucleotides was demonstrated by this group using physical techniques.

Surveillance studies conducted by H. Jick revealed that otherwise healthy females receiving oral contraceptives have a higher risk of developing thromboembolism if they are blood type A, B, or AB, as compared with blood type O. His group is operating a comprehensive drug surveillance program to obtain quantitative data on the efficacy and toxicity of drugs as they are used in hospitalized patients.

Additional findings which he also reported were (i) that elderly females have an increased tendency to bleed during heparin therapy and (ii) that intravenous ethacrynic acid, a recently marketed drug, produces gastrointestinal bleeding.

J. A. Oates reported that tricyclic antidepressant drugs will inhibit the mechanism that concentrates guanethedine in the neuron terminal and thereby prevent its pharmacologic action. The antihypertensive effect of guanethedine can be prevented when drugs such as desipramine are given concomitantly. Because methyldopa is transported into the neuron by a different mechanism, its antihypertensive action is not inhibited by therapeutic doses of desipramine in man. Amphetamine-like drugs will not only block the effect of guanethedine but will actually release it from its storage sites in the neuron.

Since publication of all the research findings supported by the Pharmacology-Toxicology Program of the National Institute of General Medical Sciences, National Institutes of Health, is anticipated, formal proceedings will not be published.

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Forthcoming Events

June

22–23. Conference on **Health Records**, Columbus, Ohio. (E. C. Stephenson, Assoc. for Health Records, P.O. Box 432, Ann Arbor, Mich. 48107)

22–24. International Conf. on the Role of **Tryptophan Metabolism in Biochemistry and Pathology**, Madison, Wis. (T. C. Meyer, Univ. of Wisconsin, Madison)

22–25. Canadian Soc. of **Agronomy**, Ottawa, Ont. (R. Loiselle, Ottawa Research Sta., Central Experimental Farm, Ottawa)

22–25. Symposium on **Bioinorganic Chemistry**, Blacksburg, Va. (R. E. Dessy, Dept. of Chemistry, Virginia Polytechnic Inst., Blacksburg 24061)

22–25. National **Colloid** Symp., 44th, Bethlehem, Pa. (S. I. Connor, Lehigh Univ., Bethlehem 18015)

22–25. Canadian Soc. of **Horticultural Science**, Ottawa, Ont. (E. C. Lougheed, Dept. of Horticulture, Univ. of Guelph, Guelph, Ont.)

22–25. American Assoc. of **Petroleum Geologists**, Calgary, Alta., Canada. (J. M. Browning, Tenneco Oil and Minerals, P.O. Box 1051, Calgary)

22–25. Canadian Soc. of **Soil Science**, Ottawa, Ont. (A. R. Mack, Central Experimental Farm, Ottawa)

22–25. **Thyroid** Conf., 6th annual, Vienna, Austria. (R. Hofer, c/o Wiener Medizinische Akademie, Alserstrasse 4, A-1090, Vienna)

22–26. American Assoc. of **Avian Pathologists**, Inc., Las Vegas, Nev. (G. H. Snoeyenbos, Univ. of Massachusetts, Amherst 01002)

22–27. **Mathematical Statistics and Probability**, 6th, Berkeley, Calif. (E. L. Scott, Dept. of Statistics, Univ. of California, Berkeley 94720)

23–26. State of the Art in **Corrosion Testing Methods** Symp., Toronto, Canada. (W. H. Ailor, American Soc. for Testing and Materials, Reynolds Metals Co., 4th and Canal Sts., Richmond, Va. 23218)

24. **Biometric** Soc., Western North American regional, Berkeley, Calif. (J. S. Williams, Statistical Lab., Colorado State Univ., Fort Collins 80521)

24–26. National **Aeronautics and Space** Administration, Ames Research Center, Moffett Field, Calif. (M. R. Heinrich, NASA, Ames Research Center, Moffett Field 94035)

24–26. American **Automatic Control** Conf., Atlanta, Ga. (D. Lyons, Dept. of Textiles, Clemson Univ., Clemson, S.C.)

24–26. **Equipment Manuals** Symp., Washington, D.C. (R. Post, Dept. of the Army, Materiel Command, Washington, D.C. 20315)

24–26. **Extreme Environments**: Microbial Adaptation. (M. R. Heinrich, Natl. Aeronautics and Space Administration, Ames Research Center, Moffett Field, Calif. 94035)

24–26. Canadian **Wood Chemistry** Symp., 3rd, Vancouver, B.C. (D. A. I. Goring, Pulp and Paper Research Inst. of Canada, 570 St. John's Rd., Pointe Claire, P.Q.)

24–27. **Drugs and Cerebral Function** Symp., 2nd annual, Denver, Colo. (M. L. Smith, Suite 1120, 2045 Franklin, Denver 80205)

24–27. **Hydrobiology**, natl. symp., Miami Beach, Fla. (J. C. Warman, Water Resources Research Inst., Auburn Univ., Auburn, Ala. 36830)

24–27. Western Soc. of **Malacologists**, 3rd annual, Stanford, Calif. (C. Skoglund, 3846 E. Highland Ave., Phoenix, Ariz. 85018)

24–1. International Symp. on **Mechanical Properties and Processes of the Mantle**, Flagstaff, Ariz. (L. R. Sykes, Columbia Univ., Palisades, N.Y. 10964)

25–27. **Leukocyte Culture** Conf., 5th, Ottawa, Canada. (J. Harris, Ottawa General Hospital, Ottawa 2)

25–1. International Conf. on **Elementary Particles**, Lund, Sweden. (G. von Dardel, Fysiska Institutionen, 3B 223 63, Lund)

28–2. **Health Physics** Soc., 15th annual, Chicago, Ill. (W. J. Blair, Biology Dept., Battelle Northwest, Richland, Wash. 99352)

28–4. American **Library** Assoc., Detroit, Mich. (D. H. Clift, Executive Director, The Association, 50 E. Huron St., Chicago, Ill. 60611)

28–4. American **Optometric** Assoc., 73rd annual congr., Honolulu, Hawaii. (G. Allen, Jr., 7000 Chippewa St., St. Louis, Mo. 63119)

28–4. **Radiation Research**, 4th intern. congr., Evian, France. (J. F. Duplan,