grase, the DNA is inserted at random into the host chromosome. Study of recombination in this viral system may provide hints to the mechanism of possibly similar events (called "*illegitimate*" because they occur between nonhomologous DNA's), such as the formation of specialized transducing phages, and of chromosomal deletions, insertions, and inversions.

Several papers in the next few sessions were concerned with techniques for correlating genetic and physical exchanges in recombinational events. Results from such studies of *E. coli* conjugation (O. Siddiqui and M. Fox, Massachusetts Institute of Technology), P22 transduction (J. Ebel-Tsipsis, Harvard Medical School), and the *E. coli* and bacteriophage lambda recombination systems (R. White and M. Fox, Massachusetts Institute of Technology) provided evidence as to which exchanges involved single-strand and which involved double-strand events. These and other related reports provided further details concerning the nature of the reactant molecules, the relative size of the exchanged DNA, and the degree of overlap in heterozygous regions in various test systems.

In the final sessions, the current status of research on the enzymology of recombination was discussed. It became clear that genetic recombination is only one facet of nucleic acid metabolism, and that the large degree of overlap with the biochemistry of DNA replication and repair will make it impossible to study any one of them alone. This point was further emphasized by the mounting evidence (genetic, physical, and biochemical) that a critical step in the termination of replication and recombination pathways may involve similar if not identical intermediate structures. It was a measure of success of this meeting that the realization of such possibility came through consideration of results from many different experimental approaches and with such diverse systems as the eukaryotic virus SV40 (A. J. Levine, Princeton University), bacteriophages S13 (J. Doniger, Brandeis University), and lambda (J. Zissler; L. W. Enquist and A. Skalka, Roche Institute of Molecular Biology; F. Stahl, University of Oregon). To date, attempts to correlate the properties of the recombination enzymes, as revealed by studies in vitro, with the proposed pathways for recombination in vivo have been less than successful. However, these studies have a great potential since the discovery of additional components of the recombination systems coupled with further studies in vivo should provide more clues to the sequence of recombinational events in the cell.

About 70 investigators participated in the symposium. The Roche Institute has published a collection of abstracts of the symposium, along with the names of all participants, which is available (on request) to anyone interested in obtaining more detailed information on the proceedings.

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Pharmacology and Toxicology Applied to the Treatment of Patients

It is encouraging that more physicians are applying recently developed principles of pharmacology and toxicology to the treatment of patients. This thought was prevalent at the Third Pharmacology-Toxicology Program Symposium, sponsored by the National Institute of General Medical Sciences of the National Institutes of Health, in Washington, D.C., 24 and 25 May 1973.

The symposium workshops were devoted to discussions of research that could aid in improving drug therapy. For example, physiological changes associated with human development create a number of problems in drug therapy. We cannot expect the same patient to react the same way to the same dose of the same drug during pubescence as during senescence. An interesting hypothesis was advanced by T. Guenthner and G. Mannering (University of Minnesota) about cytochrome P-450 and mixed-function oxidase activity in fetal and newborn liver. The induction by phenobarbital of the mixed-function oxidase system in the fetus and the pregnant female is muted. Guenthner and Mannering proposed that this effect may be due to a repressor that is displaced or metabolized in response to pretreatment with 3-methylcholanthrene (3MC). Experiments in which fetal and pregnant rats were given phenobarbital and 3MC, alone or in combination, showed that prior treatment with 3MC permitted phenobarbital to induce the mixed-function oxidase system.

A research team led by B. Mirkin (University of Minnesota) cautioned about relations between concentrations of digoxin in plasma and clinical efficacy or toxicity in the child. Both the maximum concentration of digoxin in the plasma and the rate that the plasma digoxin concentration decreased were independent of the route (intramuscular, oral, or intravenous) of digoxin administration. A relation of digoxin dose to its concentration in plasma was also noted. It was pointed out that digoxin concentrations can be used to detect an inappropriate dose regimen of digoxin but that high concentrations of digoxin in plasma may have little relation to clinical toxicity.

A significant effort is being made to better understand the principles of pharmacology and toxicology as they relate to cardiovascular diseases. The usefulness of plasma concentrations of drugs in the treatment of cardiovascular disease was emphasized. Measurement of plasma concentration of procainamide was evaluated as an adjunct in dosage management for the therapy of exercise-induced arrhythmias. J. Oates (Vanderbilt University) and his associates described a new method for measuring the plasma concentration of guanethidine, permitting more accurate evaluation of the renal clearance, pharmacokinetics, and design of an appropriate dosage regimen.

In a number of studies, special advantage was taken of the distribution of various drugs to design isotopically labeled compounds to be used for diagnostic purposes. Specifically, drugs that associate with heart tissue are labeled with gamma-emitting isotopes for possible use in noninvasive evaluation of cardiac disease.

Although drugs are metabolized by many enzymic reactions, many investigators focused their research on drug clearance by the liver oxidative enzymes. Interest was prominent in comparisons of routes of drug metabolism among different species, including man. For example, hepatic oxidative metabolism of diazoxide yielded a hydroxymethyl product in dog, man, and monkey. This was further oxidized to

carboxylic acid in vivo; rodents were unable to form the hydroxymethyl product. The metabolism of some drugs yielded multiple products. A good example is 17α-ethynylestradiol, which is converted to about eight different metabolites, varying markedly in relative amounts in rat and dog (beagle). One product, *d*-homoestrone, was formed by dog, but not by rat, liver microsomes.

Studies of drug interactions continue to yield important information. Drugs like ephedrine were shown to speed the rate of blood clearance of other drugs like dexamethasone, possibly by altering its rate of biotransformation. Other drugs have similar effects but may act, like phenobarbital, by altering hepatic blood flow. Phenobarbital was reported to increase hepatic blood flow up to 30 percent, thereby increasing hepatic drug clearance and altering body distribution and metabolism of almost any drug present in the patient's blood.

The importance of knowing all drug metabolites and their biological significance was stressed by many studies. Overdoses of glutethimide, for example, caused toxic manifestations that did not correlate well with the concentrations of glutethimide in the plasma. Upon examination, it was found that a hydroxy metabolite is formed, with a potency twice that of the parent drug. It can reach much higher concentrations than those of glutethimide when large doses are administered, thereby causing toxic manifestations. However, when normal doses are given, the concentrations of the metabolite are very low.

The objective of clinical pharmacology and toxicology is better patient care. Research efforts in this area are directed toward improving the safety of drugs by recognizing and eliminating the causes of undesirable drug effects. In addition, biochemical studies of pathways of drug metabolism have generated ingenious new treatments for previously untreatable diseases.

Immunoglobulin D antibodies to penicillin may be important mediators of nonanaphylactoid but serious reactions to penicillin, such as exfoliative dermatitis, serum sickness, and the potentially fatal Stevens-Johnson syndrome, according to J. R. Caldwell (University of Florida).

Hematologic toxicity has severely limited the use of chloramphenicol, an otherwise effective antibiotic. Adel A. Yunis (University of Miami) and his colleagues have studied the reversible and irreversible effects of this drug on bone marrow cultures. Chloramphenicol and its sulfur-containing analog exert a dose-related but reversible suppression of bone marrow cells by inhibiting synthesis of mitochondrial proteins. An irreversible suppression of mitochondrial protein synthesis in bone marrow cells is thought to be caused by an alteration of DNA synthesis in genetically predisposed patients that is caused by the para-nitro group of chloramphenicol.

Treatment for the porphyrias in man has been lacking. T. R. Tephly (University of Iowa) and his colleagues reported results of research that may lead to the prevention of serious and painful attacks of this disease. Metabolic studies have indicated that all porphyrias are associated with a derangement of the heme biosynthetic pathway. This results in an accumulation of various intermediates instead of the end product, which should be hemoprotein. Using sodium benzoate and para-aminobenzoic acid, Tephly and his associates diverted glycine away from heme biosynthesis to hippurate synthesis. The clinical and biochemical manifestations of porphyria in animals were thus ameliorated. Both sodium benzoate and para-aminobenzoic acid have been safely used in humans for other disorders. Based on a firm biochemical foundation, this clever and apparently safe pharmacologic method of control of porphyria may soon be used to treat humans.

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Forthcoming Events

April

22–25. American Acad. of **Pediatrics**, Bal Harbour, Fla. (R. G. Frazier, 1801 Hinman Ave., Evanston, Ill. 60204)

22–26. Conference on **Anomalous Scattering**, Intern. Union of Crystallography and Commission on Crystallographic Apparatus, Madrid, Spain. (S. C. Abrahams, Bell Labs., Murray Hill, N.J. 07974)

22–26. European Conf. on **Electrotechnics**, Inst. of Electrical and Electronics Engineers and Natl. Societies of Electrical