TRH. One cell line was used to study the biological and binding activities of more than 40 peptide analogs of TRH. The potential utility of the prolactin and growth hormone releasing cell system for testing the activity of physiologically important regulators of prolactin and growth hormone production, in studying the mechanisms of action of these substances in a defined and easily controlled environment, and in providing a system in which to test analogs of steroid, peptide, and alkaloid regulators that might prove useful as pharmacological agents was emphasized.

Developments in the field of drug metabolism were discussed in the presentation, "Biotransformations in mammals—a perspective," by R. E. McMahon (Eli Lilly Research Laboratories). Early work with the metabolite 4-transhydroxyethinylcyclohexylcarbamate, involving its degradation and comparison to known synthetic compounds, required a year for completion. More recently, *d*-propoxyphene metabolism has been studied in man with the aid of combined gas chromatography–mass spectrometry and heavy isotopes in approximately 1 to 2 months. Other examples of the use of analytical technology in drug metabolism studies were given. The structure of mammalian acronycine metabolites was elucidated by mass spectral and nuclear magnetic resonance techniques. Extremely small quantities of material were sufficient for this determination of structure.

In a somewhat unique combination of the fields of alkaloid chemistry and mammalian drug metabolism, S. Teitel (Hoffmann-LaRoche) described research efforts on alkaloids in mammalian systems. Alkaloids presumably form in a stereospecific fashion by enzyme-catalyzed Pichtet-Spengler condensations of amino acids and biogenic amines to form various hydroxy-substituted tetrahydroisoquinolines and tetrahydro-β-carbolines. Condensation products of L-dopa, its two mono-*O*-methyl ethers, L-tryptophan, and its 5-hydroxy derivative with formaldehyde and acetaldehyde were characterized. Additional work with the benzylisoquinolines, including oxidative coupling experiments to form aporphines, was described. The potential for forming these compounds in vivo, as well as the possibility that they possess biological activity, was discussed.

D. M. Jerina (National Institutes of Health) summarized findings from his laboratory and others on the biological formation and disposition of arene oxides. He emphasized that drugs and other environmental chemicals are metabolically activated by the formation of arene oxides which may rearrange to phenols, be hydrated to diols, become conjugated with glutathione, or react with nucleophilic sites on macromolecules. Because arene oxides are highly reactive compounds, it has been difficult to demonstrate that they are enzyme-generated intermediates. Indirect criteria such as the formation of dihydrodiols and mercapturic acid precursors as well as intramolecular migrations accompanying aryl hydroxylation (the NIH shift) have been used to support this mechanism. Chemical and enzymatic factors controlling the formation, lifetime, and disposition of arene oxides within the cells were discussed.

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JOHN P. ROSAZZA
Division of Medicinal Chemistry and Natural Products, College of Pharmacy, University of Iowa, Iowa City 52242

Genetic Recombination: Genetic, Physical, and Biochemical Aspects

Recent advances in the understanding of genetic recombination have resulted from experimental work in diverse areas of molecular biology. The Symposium on Genetic Recombination, held at the Roche Institute of Molecular Biology (2 to 4 May 1973), brought together scientists whose work represents some of the more important research directions in this field.

In the opening sessions new results obtained from genetic analyses in eukaryotic as well as prokaryotic organisms were considered. These included the analysis of gene conversion in unselected populations of meiotic tetrads of yeast (S. Fogel, University of California, Berkeley) and genetic evidence for a correction mechanism and the formation of hybrid DNA during recombination in *Ascobolus immersus* (J. L. Rossignol, Université de Paris-Sud, Orsay, France). Both systems have the distinct advantage that all the products of a single recombination event can be recovered and analyzed. Genetic analysis of recombination in viruses and prokaryotes indicate that gene conversion (unequal recovery of parental markers) occurs in these systems also (T. Boon, Institut Pasteur, Paris, France) and a molecular mechanism, based on possible repair of "mismatched" bases has been proposed. Whether there are separate enzymes involved in this phenomenon, analogous to those known for ultraviolet repair, remains to be elucidated. The technology available in prokaryotic systems should be adequate to answer this question in the near future.

Other topics in these sessions dealt with what might be called the "genetics of genetic recombination systems." A. J. Clark (University of California, Berkeley) presented results which indicate that there are at least two pathways of general recombination for *Escherichia coli* (revealed by the *rec* mutations A, B, C, F, and L, and *sbc*A) and suggested ways in which they could be interconnected. A separate and distinct system for general recombination is encoded by bacteriophage lambda (J. Zissler, University of Minnesota). A second class of recombination, responsible for the incorporation of viral genetic material into the chromosome of the host, is typified by the site-specific *int-xis* system of lambda, and was discussed by A. Campbell (Stanford University), H. Echols (University of California, Berkeley), R. A. Weisberg (National Institutes of Health), and M. E. Gottesman and S. Gottesman (National Institutes of Health). Zissler has proposed that other genes or sites in the recombination region of lambda, called delta and epsilon, may be involved in site-specific recombinational events. Several workers discussed another lambda gene, gamma, whose product interacts with the host B,C nuclease and which affects both the recombinational and replicative pathways of the viral DNA. The studies of A. I. Bukhari (Cold Spring Harbor Laboratory) on the reaction involved in the integration and excision of the DNA of phage Mu show that this process is only half site-specific. Though the crossover point on the viral DNA is fixed, and presumably contains a site recognized by the Mu inte-

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.

ANN SKALKA, ARTHUR WEISSBACH
PAUL BARTL
Roche Institute of Molecular Biology, Nutley, New Jersey 07110

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