since there are occasional trivalent carbon atoms and quadrivalent nitrogens.

HENRY C. STAEHLE
KODAK RESEARCH LABORATORIES,
EASTMAN KODAK COMPANY

DRUGS AND CELL CATALYSTS

The Interaction of Drugs and Cell Catalysts. By FREDERICK BERNHEIM. 85 pp. Minneapolis: Burgess Publishing Company. 1942. $2.25.

THE author of this limited review has summarized the principal literature concerning the *in vitro* interaction of certain selected drugs and cell catalysts in order to attempt a correlation of pharmacological action, and the fate of drugs in the body, with enzyme action. No claim is made for a complete survey of the field. Certain chemical compounds ordinarily termed "drugs," such as the indifferent narcotics, the vitamins and the hormones, are purposely excluded from consideration.

This review, although somewhat less complete than the title might indicate, is perhaps timely and should be studied carefully by all writers and teachers who are concerned with drug actions. It can be recommended heartily to those in this class who have yielded to the temptation to bridge the enormous gaps in our present knowledge concerning the reactions of cells to changes in their chemical environment by dogmatically invoking "enzyme actions."

The critical reader can not finish many sections of this review without being conditioned, by repetition, to the fact that correlations between pharmacological and enzyme action apply, for the most part, in isolated instances only, and under strict and limiting conditions of dosage, physiological state, animal species, etc. A few notable exceptions such as cyanide and physostigmine prove the rule. The evidence, for example, which relates the pharmacological actions of cyanide to its inhibiting effect on cytochrome oxidase, and physostigmine to its inhibitory action on cholinesterase, is definitive and convincing. On the contrary, as the author infers, a generalization such as the one which invokes the cholinesterase mechanism to explain all the diverse pharmacological actions of morphine, strychnine, curare and methylene blue is premature and unjustified on the basis of the facts now available.

Some reasonably good correlations are possible regarding the *in vivo* degradation of certain drugs as a result of enzymic catalysis. The hydrolytic deacetylation of heroin by a specific esterase and the oxidation of alcohol by a liver oxidase are good examples.

The author, a pioneer in the field of which he writes, takes the only position which appears to be tenable at the present time, *i.e.*, he reviews the facts, indicates the possible mechanisms which may be involved, suggests trends and methods of study and carefully refrains from personal opinions and from broad generalizations. He is frank to admit that one of the principal purposes of this review is to invite greater investigative effort in this field. The review will be welcomed by those engaged in this line of endeavor and should provide great satisfaction to the casual reader whose search is for questions, rather than answers.

M. H. SEEVERS
UNIVERSITY OF MICHIGAN

SPECIAL ARTICLES

THE LETHAL EFFECT OF TRIETHYLENE GLYCOL VAPOR ON AIR-BORNE BACTERIA AND INFLUENZA VIRUS[1]

IN an attempt to gain further insight into the mechanism of the bactericidal and viricidal action exhibited by propylene glycol vapor for air-borne disease agents[2, 3] a number of glycols and related compounds were tested with the same techniques employed in the studies on propylene glycol. Among the compounds investigated were other members of the aliphatic glycol series such as ethylene glycol, diethylene glycol, triethylene glycol, trimethylene glycol, dipropylene glycol, various butylene glycols, a number of aliphatic and aromatic ethers, alcohols, ketones and amines and compounds containing various combinations of these active chemical radicals.[4] Some of these substances were found to be fully as effective as propylene glycol and several of them considerably more lethal for air-suspended bacteria. However, with two notable exceptions most of these latter compounds were unsuitable for practical use because in the concentrations required they were toxic or possessed a disagreeable odor. The two substances which exhibited a high degree of germicidal potency and were odorless were triethylene glycol and dipropylene glycol. There is not much data available on the

[1] This investigation was aided in part through the Commission on Cross Infections in Hospitals, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of the Surgeon General, U. S. Army.

[2] O. H. Robertson, E. Bigg, T. T. Puck and B. F. Miller, *Jour. Exp. Med.*, 75: 593, 1942.

[3] O. H. Robertson, C. G. Loosli, T. T. Puck, E. Bigg and B. F. Miller, SCIENCE, 94: 612, 1941.

[4] A detailed record of these experiments together with a theoretical analysis of the mechanism of action of glycol vapors will be presented elsewhere.

toxicity of triethylene glycol and less on dipropylene glycol, but preliminary tests by several investigators[5, 6, 7] have shown that triethylene glycol is among the least toxic of the glycols, comparing favorably in this respect with propylene glycol. Since triethylene glycol[8] vapor produced bacterial killing in even more minute concentration than dipropylene glycol, this compound has received especial study.

The experimental tests were carried out both in the small glass chambers previously described[2] and in an experimental room of 800 cubic feet capacity. Since the amounts of triethylene glycol found to be effective were so small, greater experimental accuracy was obtained in the experimental room where most of the tests were conducted. A satisfactory apparatus for the vaporization of this glycol into the room consisted of a small aluminum cup 2–3 cc capacity seated on and heated by a radio resistor carrying 15–20 volts. 0.1 cc to 0.2 cc of triethylene glycol evaporated completely in 3–5 minutes. The experimental procedure was as follows: microorganisms separated from their culture fluid and resuspended in fresh unsterile saliva were atomized into the center of the room in numbers sufficient to yield hundreds to thousands of colonies on blood agar plates exposed on the floor of the room for a period of ten minutes. The first plate was opened immediately after the bacterial spray and

TABLE 1

EFFECT OF TRIETHYLENE GLYCOL VAPOR ON AIR-BORNE PNEUMOCOCCI AND HEMOLYTIC STREPTOCOCCI

Time intervals after introduction of bacterial suspension	Number of colonies on settling plates		
	Strepto-coccus	Pneumo-coccus	Pneumo-coccus control
Immediately after	297	860	953
10 minutes	237	628	871
30 minutes	134	460	500
40–45 minutes	Triethylene glycol vapor introduced in concentration of 1 : 100,000,000	1 : 200,000,000	No vapor
45 minutes (immediately after vapor)	2	15	527
55 minutes	1	0	457
75 minutes	0	0	329

three others at ten-minute intervals. Then as soon as the last control plate was closed triethylene glycol was introduced from the vaporizing apparatus placed beforehand in the center of the room, over a fan throwing a gentle breeze in a vertical direction which caused effective mixing of the air in all parts of the room. Immediately following the termination of vaporization the first test plate was uncovered. The others followed at 10-minute intervals.

A protocol of two experiments, one with pneumococcus Type I and one with Beta hemolytic streptococcus group A is shown in Table 1. Concentrations of 1 gram of triethylene glycol in 100 million cc of air and 200 million cc of air respectively (0.2 and 0.1 cc of the glycol in 800 cubic feet of air), caused almost immediate disappearance of the streptococci and pneumococci from the air and within 10 minutes the plates were essentially sterile. As a further means of testing the sterility of the air a 2 to 3 cubic foot sample of the room air was drawn through the Moulton air sampler[9] ten minutes after the introduction of the vapor. Such samples of air were found to be sterile in both instances. Dilutions of triethylene glycol as high as 1 to 600 million were found to exert a definite killing effect on pneumococci and a group C streptococcus. A number of controls conducted both before and after the tests showed that pneumococci and streptococci dispersed into the air of the experimental room in fine droplet form gradually diminished in numbers over a period of 6 to 7 hours. By the end of 1–2 hours approximately 40 per cent. of the original number were still recoverable.

Tests with the mouse-adapted influenza virus A were conducted in the same manner as those with bacteria except for the fact that Swiss mice were employed. The technique for producing experimental influenza in mice has been described elsewhere.[10, 3] During the control period the mice were exposed for 20 minutes to the infected air of the room beginning

TABLE 2

EFFECT OF TRIETHYLENE GLYCOL VAPOR ON AIR-BORNE INFLUENZA VIRUS

Time intervals after introduction of virus suspension	Mice exposed to virus-containing air (2.5 cc of 10^{-1} virus suspension sprayed into 800 cubic foot room).	Result	Control on duration of viability of air-suspended virus
10 minutes	20 mice	All 40 died— Influenzal pneumonia	20 mice
24 minutes	20 mice*		20 mice* All 40 died
30–35 minutes	Triethylene glycol vapor introduced in concentration of 1 : 200,000,000		No vapor
45 minutes (10 minutes after vapor)	40 mice†	All survived— No pulmonary lesions	40 mice† 37 died, 3 killed, 14 days— Extensive pulmonary lesions

* Room air drawn for six minutes through desiccating jar containing mice. Jar then sealed. Mice removed from jar after twenty minutes.
† Twenty of these exposed in desiccating jar as above.

[5] W. M. Lauter and V. L. Vrla, *Jour. Am. Pharm. Asn.*, 29: 5, 1940.

[6] A. R. Latven and H. Molitor, *Jour. Pharm. and Exp. Therap.*, 65: 89, 1939.

[7] H. F. Smyth, J. Seaton and L. Fischer, *Jour. Indust. Hyg.*, 23: 259, 1941.

[8] The triethylene glycol used in this study was kindly furnished by the Carbide and Carbon Company.

[9] S. Moulton, T. T. Puck and H. M. Lemon, SCIENCE, 97: 51, 1943.

[10] C. G. Loosli, O. H. Robertson and T. T. Puck, *Jour. Inf. Dis.* In press.

at 10 minute and 24 minute intervals after introduction of the virus as shown in Table 2. The first group of mice was simply placed in the room and allowed to remain there for 20 minutes. At the 24-minute period a desiccator jar containing a second group of mice was filled with air from the room and then sealed for 20 minutes. At the end of 30 minutes triethylene glycol was introduced. A period of ten minutes was then allowed for thorough mixing of virus and vapor following which normal mice were introduced in the room. It was found that as small a concentration of triethylene glycol as 1 gram in 200 million cc of air protected mice completely against an amount of airborne virus which a short time before had caused death of all the exposed (control) mice. Control tests on the persistence of influenza virus in the air showed that for 40 to 60 minutes after its introduction sufficient virus remains in the air to kill over 90 per cent. of the mice so exposed.

The above experiments on pathogenic bacteria and influenza virus were repeated many times with essentially identical results. While different pathogens as well as certain non-pathogens exhibited slight differences in sensitivity to triethylene glycol vapor, marked bactericidal action was obtained with dilutions of 1 gram of glycol in 100 million to 200 million cc of air. Tests on the oral toxicity of triethylene glycol for monkeys and rats and exposure for prolonged periods of time to vapors of this compound are being carried out.

O. H. ROBERTSON
THEODORE T. PUCK
HENRY F. LEMON
CLAYTON G. LOOSLI

DEPARTMENT OF MEDICINE,
UNIVERSITY OF CHICAGO

PREVENTING THE BACTERIAL OXIDATION OF RUBBER[1,2]

THE recent article by ZoBell and Grant[3] notes the attack of rubber by bacteria under conditions of high moisture. It is suggested that "the life of rubber products which come in contact with moisture may be prolonged if ways can be found to retard or prevent the activity of rubber oxidizing microorganisms."

In the compounding of rubber commercially, native rubber is mixed with a number of chemicals, each of which serves a specific purpose in the properties of the finished product. Among these are the accelerators[4] which lower the temperature and shorten the time for vulcanization and lengthen the life of rubber.

Two well-known accelerators are mercaptobenzothiazole and tetramethylthiuram disulfide. These compounds[5] have been tested for their ability to inhibit germination of fungi, and gross observations have been made on their ability to inhibit bacterial growth. Mercaptobenzothiazole, known to the rubber industry as Captax, is a moderately good fungicide, and tetramethylthiuram disulfide, known as Tuads, is excellent. The latter compound is now being marketed under still another trade name as a seed protectant and for the prevention of turf diseases. Both of these materials have been tested under the field conditions prevailing in Connecticut by the authors for their efficacy in controlling plant diseases. Mercaptobenzothiazole, while inferior to tetramethylthiuram disulfide, has given partial plant disease control.

These materials, when employed in the compounding of rubber, are intimately mixed with zinc oxide, which is itself a useful fungicide and seed protectant. From a knowledge of the formulae of these accelerators, it occurred to the authors that zinc oxide might react with mercaptobenzothiazole and with tetramethylthiuram disulfide and that the reaction products might differ in their anti-microbial potency.

Spore germination tests were set up, using the method of Horsfall, *et al.*[6] Glass slides were sprayed with aqueous suspensions of mercaptobenzothiazole and tetramethylthiuram disulfide, with and without zinc oxide, and with suspensions of zinc oxide alone. Each type of suspension was sprayed in a dosage series. The glass slides were allowed to dry, after which drops of a suspension of spores of the fungus, *Macrosporium sarcinaeforme,* were placed on the

TABLE 1

EFFECT OF ADDING ZINC OXIDE TO MERCAPTOBENZOTHIAZOLE ON THEIR ABILITY TO INHIBIT THE GERMINATION OF FUNGOUS SPORES

Dosage of toxicant (γ per sq. cm)		Percentage inhibition
Mercaptobenzothiazole		
864		100
432		96
216		4
108		1
Mercaptobenzothiazole + zinc oxide		
520	345	4
260	173	2
130	86	0
65	43	0
Zinc-oxide		
864		100
432		100
216		98
108		94

[1] Contributions from the Department of Botany, University of Nebraska, N. S. No. 138, and published with the approval of the director of the Connecticut Agricultural Experiment Station.

[2] Part of the data reported were obtained in the Department of Plant Pathology and Botany of the Connecticut Agricultural Experiment Station. The remainder were obtained at the University of Nebraska.

[3] Claude E. ZoBell and Carroll W. Grant, SCIENCE, 96: 379, 1942.

[4] Paul I. Murrill, *Chem. and Eng. News,* 20: 1361, 1942.

[5] We are indebted to Mr. F. E. Hutchins of R. T. Vanderbilt Company, 230 Park Ave., New York City, for supplying us with these compounds as well as the specially purified grade of zinc oxide used in the rubber industry.

[6] James G. Horsfall, J. W. Heuberger, E. G. Sharvelle and J. M. Hamilton, *Phytopath.,* 30: 545, 1940.