with penicillin appears to be of importance only when recovery is dependent upon the early, rapid killing action of penicillin. A recent report of apparent interference of aureomycin with penicillin in pneumococcal meningitis is therefore of great interest(7). This is a condition which, untreated, is associated with a high mortality rate, and in which phagocytosis is relatively ineffective(8).

The importance of the interference of the newer antibiotics with the early killing action of penicillin can be determined only by extensive clinical studies. However, on the basis of the present experiments and the evidence cited above, it is our impression that there are probably few clinical conditions in which the phenomenon is of practical importance.

Summary. 1. Mice were infected with group A streptococci and treated with chloramphenicol and penicillin, separately and in combination. Jawetz's observation that chloramphenicol interfered with penicillin when animals were given a single aqueous injection of both antibiotics was confirmed. 2. The interference was not demonstrable, however, when antibiotic blood levels were maintained for 2 or 3 days. Thus, despite early interference, the combination caused a progressive bactericidal action which, in conjunction with phagocytosis, protected the mice as well as penicillin alone. 3. These experiments imply that the phenomenon of antibiotic interference is seldom of clinical significance.

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Inhibition of Mouse Encephalomyelitis Virus, *in vitro*, by Certain Nucleoprotein Derivatives.* (19450)

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Previous work showed that various substances including heavy metals, enzyme inhibitors such as dinitrophenol, cyanide, azide and iodoacetate as well as certain amino acids and analogues inhibit the propagation of Theiler's GDVII strain of murine encephalomyelitis virus in tissue cultures of minced one-day-old mouse brain(1-3). The present report gives the results of tests with certain purines, pyrimidines and substituted pyrimidine nucleosides(4-6). Preliminary data have been presented in part elsewhere(7).

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Materials and methods. Cultures were prepared in 50 ml Erlenmeyer flasks closed with rubber stoppers and containing 3 ml of Simms' X7 solution and 50-100 mg of minced mouse brain from one-day-old mice. The initial reaction of the medium was adjusted to pH 8-9. Cultures were incubated for 1-2 days at 35°-36°C. The supernatant fluid obtained after centrifugation of the pooled material from 3 flasks was tested for virus content by hemagglutination of human red blood cells with serial twofold dilutions(3).

Results. Several of the compounds tested

TABLE I. Percentage Reduction in Hemagglutination Titers of Virus, *In Vitro*, in the Presence of Certain Compounds in Comparison with Control Cultures.

Compound tested	mg/ml	% reduction in titer
Adenine	.5	0
"	1	87–100
Adenosine	1	75
"	3	100
Adenylic acid	3	0
Cytidilic "	3	0
Cytidine	1	0
"	3	75–87
Guanine	3	0
Guanosine	1	50
Guanylic acid	1	0
Thymine	1	0
"	3	87
Uracil	3	0
Uridine	3	0
5-Aminouridine	.2	0
"	.5	75–87
"	1	87–100
5-Bromouridine	1	50
5-Chlorouracil	1	0
5-Chlorouridine	.1	0
"	.3	50
"	.5	75
"	1	87–100
2,6-Diaminopurine	1	100
Diazouridine	.5	50
"	1	75–87
5-Formamidouridine	.5	50
"	1	50
Glucosylthymine*	1	0
Glucosyluracil*	1	0
5-Hydroxyuridine	.1	0
"	.3	75
"	.5	75
"	.7	94
3-Methyluridine	1	50
Ribosylthymine*	1	0

* Pyranose ring structure.

inhibit virus propagation (Table I). Attempts were made to reverse the inhibition of uridine substituted compounds by addition of various substances. Only uridine caused a partial reversal of inhibition (Table II). This represents the first example of what apparently is competitive metabolism found so far with this system. Guanine, 1 mg/ml, did not reverse the inhibition produced by 2,6-diaminopurine, 1 mg/ml; methionine, 3 mg/ml did not prevent inhibition by adenine, 1 mg/ml.

The effects of 5-chlorouridine, *in vivo*, on virus infection were tested in the following manner: 3 weeks old mice weighing less than 15 g each were inoculated intracerebrally with 0.03 ml of a 10^{-5} dilution of tissue culture virus (2 M.L.D.). Thirty mg of 5-chlorouridine contained in 0.5 ml volume were injected intraperitoneally 6, 30 and 54 hours after virus inoculation. The control group of mice received saline instead of 5-chlorouridine. Mice died of encephalitis on the days after virus injection as follows: test group, 2,6,6,6,6, 7,7,8,8,9; control group, 3,6,6,6,6,6,7,7,7 (1 survivor). The same results were obtained if the first dose of drug was given one-half hour before the virus injection and the second and third doses were given 24 and 48 hours later, respectively. 5-Chlorouridine had no curative effect. Larger doses were not used since it was found in other tests that a single injection of 45 mg was lethal for mice of this age.

Discussion. Some compounds which are known to interfere with nucleic acid biosynthesis also inhibit growth of bacteria and fungi(5-13). The present results show that substituted pyrimidine nucleosides, which inhibit growth of *Neurospora*(5,6) also limit propagation of Theiler's virus, *in vitro*. The strain of *Neurospora* used requires uracil, cytidine or uridine for growth. That the viral inhibition may be due to a block in the pathway of virus nucleic acid synthesis is suggested by the reversal effect produced by uridine. This was also suggested to explain the inhibition of $P^{32}O_4$ uptake by the ribonucleic acid fraction of one-day-old mouse brain in the presence of 5-chlorouridine(14). Reversal of the inhibition produced by antimetabolites on the propagation of viruses has been observed by other workers. Coliphage inhibition by 2-amino-9-(p-aminophenyl) acridinium chloride is reversed by ribonucleic acid(15). Benzimidazole or 2,6-diaminopurine inhibits vaccinia virus in chick embryo tissue culture; the latter but not the former effect is reversed by adenine(16).

An inhibitory effect on the GDVII virus propagation is observed with adenine, adenosine, cytidine, guanosine and thymine. With the exception of thymine, these compounds are utilized by the rat for tissue nucleic acid synthesis. An explanation of these results is not apparent.

Summary. Adenine, adenosine, cytidine, guanosine and thymine inhibit the propaga-

TABLE II. Partial Reversal of Hemagglutination Inhibition by Uridine Derivatives. Tested with GDVII Virus in Tissue Cultures.

	% reduction of titer compared with control					
	5-Chlorouridine, 1 mg/ml		5-Aminouridine, .5 mg/ml		5-Hydroxyuridine, .3 mg/ml	
Compounds tested	Alone	Combined	Alone	Combined	Alone	Combined
Uridine, 1 mg/ml	100	75	87	60	87	50
3	87	75	—	—	—	—
Uracil, 1	94	87	87	75–87	—	—
3	—	—	75	75	—	—
Cytidine, 1	87	87	87	75	—	—
			1 mg/ml			
Uridine, 3			87	75		

tion of Theiler's GDVII strain of murine encephalomyelitis virus in tissue cultures of one-day mouse brain. Guanine, uridine, uracil, guanylic or cytidylic acids did not inhibit. Various substituted nucleosides including amino-, chloro-, diazo-, formamido-, hydroxy- and methyluridine were inhibitory. Uridine partially reversed this inhibition. 5-Chlorouracil, ribosylthymine and glucosylthymine did not inhibit; 2,6-diaminopurine did. 5-Chlorouridine was not effective against this viral infection in mice.

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Poliomyelitis Infection in Cortisone-Treated Hamsters Induced by the Intraperitoneal Route.* (19451)

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It was previously reported that cortisone enhances greatly the experimental poliomyelitis infection in the Syrian hamster(1,2). The studies embodied in this paper deal with the production of the disease in this animal by the intraperitoneal route with the aid of cortisone(3).

Experimental. Syrian male hamsters weighing 20-28 g, supplied by the Lakeview Hamster Colony and the Breeding and Laboratory Institute, and Swiss mice, CF1 obtained from the Carworth Farms, weighing 15-20 g, were employed. All the animals were observed

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