large amounts of thiamine to the diet prevented the toxicity due to oxythiamine, and the parenteral and oral administration of thiamine to oxythiamine-toxic chicks tended to overcome the inhibition.

The chick, as well as the mouse, has been shown to be very sensitive to the addition of oxythiamine to the diet. It seems probable, therefore, that oxythiamine is an antagonist of thiamine in the nutrition of all species that require this vitamin as an essential nutrient.

Evidence has been presented which indicates that the thiamine requirement of growing White Leghorn cockerels is greater in the absence of sufficient of the unidentified chick growth factors.

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The Virostatic and Virucidal Action of α-Haloacylamides on Vaccinia Virus *in Vitro*. (17365)

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During the course of an investigation dealing with the possible antiviral effects of pyrimidine derivatives[1] it was found that amides of 5-aminouracil[1] inhibit the multiplication of vaccinia virus in the tissue culture system previously described.[2] Based on antagonisms demonstrable using *Lactobacillus casei*[3] it was predicted that the climax of this series would be reached with 5-chloroacetamidouracil or amides of 5-aminouracil with other acids having pKa values near that of chloroacetic acid. Actually the activity of chloroacetamidouracil was greater by a factor of 10 or more than the predicted value. Further investigation revealed a high degree of antiviral activity to be a function of all the chloro- and bromoacylamides and dichloroacetamides which were tested including chloroacetamide itself. This paper presents the data on the *in vitro* tests.

Experimental. Screening tests with vaccinia virus in chick embryonic tissue culture were carried out as described previously.[2]

Discussion. It will be seen (Table I) that bromo- and chloroacylamides usually inhibit growth of the vaccinia virus. The inactivity of the fluoroacetamidouracil (Compound 14, Table I) suggests that an alkylation reaction may be involved in the activity.

When the high degree of activity of 5-chloroacetamidouracil was discovered attention was turned first to the embryonic tissue test system. It was a recognized weakness of the screening test that substances capable of poisoning the embryonic tissue undoubtedly would be expected to prevent the multiplication of the virus.[2] Thus known poisons, such as azide and cyanide, could be shown to inhibit viral multiplication.[2] On the other hand, 5-chloroacetamidouracil was no more toxic to mice than related substances of much lower antiviral potency. It is ineffective against the majority of bacteria, and in reasonable concentration fails to affect the respiration and glycolysis of tissue slices or the glycolysis of washed cell suspensions of *Lactobacillus casei*.†

* These studies were begun at Western Reserve University Medical School (1945) and continued at the Medical College of Virginia (1946-7).

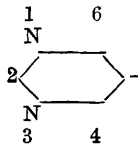
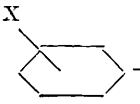
1 Thompson, R. L., Wilkin, M. L., Hitchings, G. H., Elion, G. B., Falco, E. A., and Russell, P. B., *Science*, 1949, **110**, 454.

2 Thompson, R. L., *J. Immunol.*, 1947, **55**, 345.

3 Hitchings, G. H., Elion, G. B., Falco, E. A., Russell, P. B., and Vander Werff, H., *Annals N. Y. Acad. Sci., in press.*

† We are indebted to Doris Lorz for these determinations.

TABLE I.
Virucidal Activity of Various Haloacylamides.*

No.	Formula / Compound	Ref.	Conc.† mg per 1	Increase in virus titer (logarithm) Control	Treated
1.	$ClCH_2CONH_2$		100	2.03	—1.16
	 –NHCOR Pyrimidine derivatives				
	2 / 4 / 6 / R				
2.	OH / OH / H / CH_2Cl	§	10	1.04	—1.30
3.	OH / OH / CH_3 / CH_2Cl	8	100	2.24	—1.30
4.	NH_2 / OH / CH_3 / CH_2Cl	8	100	2.24	—1.00
5.	CH_3 / OH / CH_3 / CH_2Cl	‡	100	2.24	—1.00
6.	NH_2 / CH_3 / CH_3 / CH_2Cl	§	10	2.34	—1.50
7.	Cl / H / H / CH_2Cl	§	5	2.34	—1.50
8.	OH / OH / H / $CHCl_2$	§	100	2.20	—0.43
9.	O / O / H / CH_2Cl‖	§	10	2.75	—1.79
10.	NH_2 / OH / H / CH_2Cl	§	10	1.40	—1.50
11.	NH_2 / NH_2 / OH / CH_2Cl	§	100	2.09	—1.00
12.	OH / OH / H / $CHBrCH_2CH_3$	§	100	1.89	—1.84
13.	OH / OH / H / $CHBrCH_3$	§	10	2.03	—1.16
14.	OH / OH / H / CH_2F	§	100	2.33	2.00
15.	OH / OH / H / CH_2CH_2Cl	§	100	1.85	2.02
	 –$NHCOCH_2Cl$ Anilides				
16.	H	7	10	2.75	—1.79
17.	*p* Cl	5	10	1.84	—1.82
18.	*p* MeO	5	5	1.57	—1.93
19.	*p* NO_2	5	5	1.57	—1.93
20.	*p* H_2NSO_2	6	10	2.20	—1.50
21.	*p* H_2NCO	6	10	2.12	—2.00
22.	*p* CH_3	6	100	1.76	—2.16
23.	2'Cl 5'Cl	§	100	1.76	—0.33
24.	*o* NO_2	5	100	1.76	—1.28
25.	*m* NO_2	5	5	1.57	—1.93

* Determined as described by Thompson.[2]
† The minimal effective concentration is given.
‡ We are indebted to Prof. Alex. R. Todd for this substance.
§ These hitherto undescribed compounds were prepared in The Wellcome Research Laboratories.
‖ 1,3-Dimethyl derivatives.
[5] Beckurts, H., and Frerichs, G., *Arch. Pharm.*, 1915, **253**, 233.
[6] Jacobs, W. A., and Heidelberger, M., *J. Am. Chem. Soc.*, 1917, **39**, 2429.
[7] Meyer, P. J., *Ber.*, 1875. **8**, 1153.
[8] Russell, P. B., Elion, G. B., and Hitchings, G. H., *J. Am. Chem. Soc.*, 1949, **71**, 474.

When the structure of chloromycetin (Chloramphenicol) (IV, Fig. 1) became known,[4] the relationship of this dichloroacetamide to such compounds as 5-chloroacetamidouracil (I, Fig. 1), 5-dichloroacetamidouracil (II) and α-chloro-*p*-nitroacetanilide (III) became apparent. The previous work suggests that the virucidal center of chloromycetin resides in the dichloroacetamide linkage and that all haloacylamides are potentially virucidal. It suggests the possibility that some of the simpler haloacylamides may find practical application in the sterilization of

[4] Rebstock, M. C., Crooks, H. M., Jr., Controulis, J., and Bartz, Q. R., 115th Meeting Am. Chem. Soc., San Francisco, Calif., 1949. Abstracts 9K.

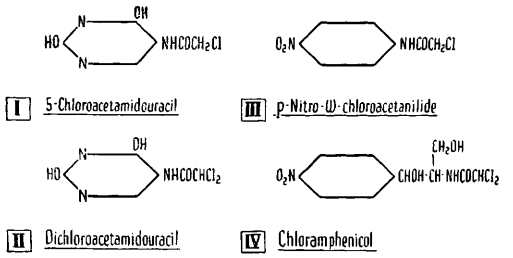


FIG. 1.

substances from the standpoint of viral contamination.

These findings suggest that the tissue culture system when properly controlled is capable of the demonstration of active virucidal chemical groupings. Virucidal substances discovered in this way may be thought of as comparable to bactericidal substances discovered in the usual *in vitro* bacterial growth systems. The relationship between such substances and useful chemotherapeutic agents may be as uncertain in the one biological system as it is in the other.

Summary. Several chloro- and bromoacylamides were demonstrated to inhibit multiplication of the vaccinia virus in chick embryonic tissue. 5-Dichloroamidouracil was found to be inhibitory whereas 5-fluoroacetamidouracil was inactive.

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Seasonal Variation in Human Fasting Blood Sugar Levels.* (17366)

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During the course of a study on human subjects involving the effect of the breakfast meal on carbohydrate metabolism,[1] seasonal variation in fasting blood sugar levels was noted.

Work done in this laboratory over a 2 year period on 9 women gave a total of 170 fasting blood sugar determinations. When these values were averaged by months, the results shown in Fig. 1 were obtained. The fasting values during the 2 year period were within the range given by Peters and Van Slyke.[2] However, they showed marked seasonal differences. Blood sugar concentration rose progressively with the colder months of the year and were definitely higher in the winter than during the summer months.

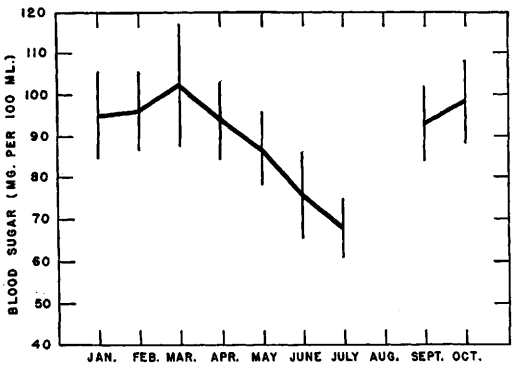

FIG. 1.

Average blood sugar values by month. Standard deviations indicated by vertical lines.

The subjects used in this study were 9 women laboratory workers ranging in age from 28 to 48 years They were of average weight and height and moderately active. They were considered to be in good health although no physical or medical examinations were made.

Periodic blood counts and urine analyses were normal. At no time did any of the subjects participate in an experiment when suf-

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1 Orent-Keiles, Elsa, and Hallman, Lois F., U.S.D.A. Circular, 1949, No. 827.

2 Peters, J. P., and Van Slyke, D. D., Quantitative clinical chemistry, Vol. 2, Chap. III, Williams and Wilkins, 1946.