TABLE II.
Mortality Rate per r. Unit—Species Differences.

Species	No. animals used	dx/dy*	Reference
Rats	500	1.2%	Clark and Uncapher
Guinea pigs	50	0.7	Ellinger[6]
Swine	32	0.5	Tullis *et al.*[10]
Mice	119	0.3	Ellinger[6]
Goldfish	774	0.08	Ellinger[9]

* x = % mortality and y = dosage in r, in the LD_{50} range.

of mortality per roentgen unit dose, in the steepest part of the mortality curves. This is an expression of the slope, dx/dy, where x represents unit per cent mortality and y the unit dose.

This means that 1.2% of the rats died per unit increment in dosage of X-rays, where the other species died at a lower rate per dosage increment.

It will be interesting to compare these data with those for the dog, rabbit, monkey, cat and other species.

It occurs to us that in studies directed toward the therapy or protection by pre-treatment of animals given total body ionizing radiation, that if the mortality curves are quite steep, as in the rat, dosages in the "LD_{50}" range may not be permissible, and that dosages should be given which consistently kill 100% of the untreated animals, so that an estimation of protection could be made by both the time required to kill 50% of each group, as shown in Fig. 3, and by the per cent final mortality. If the slope is not so steep (dx/dy is small) and if sufficient animals are used, it would be advisable to include at least 3 dosages, LD_{100}, LD_{50-60} and LD_{20-30}.

Summary. The LD_{50} for total body X-radiation in Wistar rats is 640 ± 5 r with a 30-day endpoint. The time elapsing before 50% mortality occurs at different doses is a more reliable measure of mortality than the dosage-mortality curve or the dosage-survival time curves for different X-ray doses. The dosage-mortality curve of rats has such a steep slope in the LD_{50} range that variations in mortality of from 0 to nearly 100% may occur in this range because of variations in animals and in the X-ray machine output. Therefore in studies directed toward therapy or protection of animals given total body ionizing radiation, if the mortality curves are extremely steep as in the rat, dosages in the LD_{50} range should not be used. Other measures which might be employed are discussed.

We wish to express our gratitude to Dr. F. Ellinger, Director of Radiological Research, Naval Medical Research Institute; to Dr. A. H. Dowdy, chairman, Department of Radiology, School of Medicine, University of Calif.; and to Dr. V. P. Bond and Peggy Smith of the Navy Radiological Defense Laboratory, San Francisco Naval Shipyard, for reading this manuscript and making certain suggestions.

Received April 25, 1949. P.S.E.B.M., 1949, **71**.

17139. Resemblance of a Strain of Swine Influenza Virus to Human A-prime Strains.*

THOMAS FRANCIS, JR., J. J. QUILLIGAN, JR., AND ELVA MINUSE.
From the Department of Epidemiology and Virus Laboratory, School of Public Health, University of Michigan, Ann Arbor, Mich.

In the course of studies in a group of children vaccinated with the Type A PR8 strain of influenza virus, an outbreak of influenza occurred in that population.[1] The children's sera were being tested against different strains of influenza virus, and it was

* This investigation was conducted under the auspices of the Commission on Influenza, Army Epidemiology Board, Office of the Surgeon General, U. S. Army, Washington, D.C.

[1] Quilligan, J. J., Jr., Minuse, Elva, and Francis, Thomas, Jr., *J. Clin. Invest.*, 1949, **27**, 572.

observed that the serological reactions to a strain of virus of swine origin were similar to those obtained with strains isolated during the 1947 outbreak in the civilian population of the United States.[2-4] The evidence strongly suggests that this swine strain (Oti) is closely related to strains of human origin more recently studied which are being called A-prime.

Materials and methods. Description of Virus Strains. The virus preparations used in the agglutination inhibition tests were taken from infected allantoic fluid. The passage history of each strain is as follows: Type A RP8[5]—7 ferret, 593 mouse and 69 egg passages; A-prime Rhodes[2]—4 ferret, 7 mouse, and 13 egg passages; A-prime FM1[3] (obtained from Dr. J. E. Smadel)—37 mouse and 15 egg passages; Swine 1976 (obtained from Dr. R. E. Shope)—38 mouse and 19 egg passages; Swine Oti, a strain sent to Dr. R. E. Shope by Dr. M. Tsurumi of the Imperial University of Nagoya, Japan. He, in turn, had received it from Dr. Oti, who originally isolated it from swine in Korea in 1939. Dr. Shope noted that this strain was different in its behavior from the American swine strains, and after being received in this laboratory in 1944 after 179 mouse passages it was soon realized that it acted a great deal like a type A human strain. Since then it has been passed 33 times in eggs.

Sera from Children. There were 175 children in the institution where the vaccination study was carried out; 56 recognized cases of influenza appeared among them between late February, 1947 and the middle of April, 1947. Serum had been obtained from most of the children at the termination of the vaccination study, in early November 1946, four months before the outbreak of influenza. Beginning one week after the last clinically recognized case, approximately seven months after the last previous sample, another specimen of serum was obtained from 52 children, eleven of whom had been noticeably ill during the epidemic period.

Sera from Adults. A group of 93 pairs of acute and convalescent sera were obtained from patients admitted to the student Health Service Infirmary of the University of Michigan during the period of the outbreak.[2] Fifty-eight of them had been inoculated with a vaccine of combined A and B influenza viruses.

Sera from Animals. All animal sera, with one exception, were from ferrets which received intranasal inoculations of the allantoic fluids containing the specific viruses. Sera were generally obtained before and 2 weeks after inoculation. Strict isolation technic was used and only single strains of virus were introduced into the ferret isolation unit to eliminate the possibility of cross-infection of the animals. One anti-serum prepared in rabbits (inoculated with the Oti strain in 1944) was used to check the identity of the current Oti line that was used in the tests. The results indicated that the current Oti line reacted the same as it had before any A-prime strains had been isolated in this laboratory.

Serological Tests. Antibody was measured by inhibition of agglutination of chicken erythrocytes. Four agglutinating units of virus were mixed with the serially diluted sera. A pattern method[6] of interpreting the end-point was used. The titers are expressed as reciprocals of the modified means.[7]

Neutralizing antibody was measured by inoculating mice with serially diluted serum plus 500-1,000 MLD of the virus strains. The 50 per cent endpoints[8] were calculated on the basis of the lethal effect of virus during a ten-day observation period. Titers are recorded as final dilutions of serum.

Results. An extensive examination was made of the sera obtained from the children

2 Francis, Thomas, Jr., Salk, Jonas E., and Quilligan, J. J., Jr., *Am. J. Pub. Health*, 1947, **37**, 1013.

3 Sigel, M. M., Shaffer, F. W., Kirber, M. W., Light, A. B., and Henle, W., *J.A.M.A.*, 1948, **136**, 437.

4 Smadel, J. E., *Bull. U. S. Army Med. Dept.*, 1947, **7**, 795.

5 Francis, T., Jr., *Science*, 1934, **80**, 457.

6 Salk, J. E., *J. Immunol.*, 1944, **49**, 87.

7 Quilligan, J. J., Jr., and Francis, Thomas, Jr., *J. Clin. Invest.*, 1947, **26**, 1079.

8 Reed, L. J., and Muench, H., *Am. J. Hyg.*, 1938, **27**, 493.

TABLE I.
Effect of A-prime Influenza Virus Infection on Serological Response of the Children Expressed as the Modified Mean Antibody Titers.

Sera from	Stage	No.	Modified mean titers PR8	Rho	Oti	Swine 1976
Children	Pre-infection	52	716	43	38	24
	Post-infection	52	625	160	136	35

TABLE II.
Comparison of Antibody Titers of Vaccinated and Unvaccinated Members of the University Group.

	Virus strains PR8		Rhodes		Oti		Swine 1976	
	Vac.	Unvac.	Vac.	Unvac.	Vac.	Unvac.	Vac.	Unvac.
No. of sera tested	57	35	56	35	58	35	57	35
Acute*	371	77	40	34	141	63	50	35
Conv.*	722	230	114	106	415	242	106	90
Fold—inc. in means	1.9×	3×	2.8×	3×	2.9×	3.8×	2.1×	2.6×

* Modified mean titer.

TABLE III.
Effect of A-prime Influenza Virus Infection on Serological Response of Two Groups of Individuals Expressed as the % Showing Incremental Changes in Titer.

Group	Virus strain	Decrease or no change	2-fold rise	4-fold or greater rise	Total No.
University students	PR8	30	33	37	92
	Rho	21	29	50	93
	Oti	22	26	52	93
	Swine 1976	29	41	30	91
Children	PR8	73	11	16	37
	Rho	18	22	61	51
	Oti	22	15	63	51
	Swine 1976	53	29	18	51

following repeated inoculations of the univalent vaccine.[1] It was found that but a minimal rise in antibody to the 1976 strain of swine virus occurred and the response as measured with the Oti strain was small. However, when the sera taken after the outbreak of influenza were compared with those obtained earlier a sharp increase in titer to the Oti strain was noted (Table I). There was no significant change in the low titer against the Swine 1976 strain, nor in the high post-vaccination titer against the PR8 strain. The results with the Oti strain were essentially parallel to those measured by the Rhodes strain (A-prime) isolated during the 1947 epidemic. Since all the children in the group were vaccinated with PR8 the lack of further response to that strain could be readily ascribed to the vaccination.

The group of University students who had been sick comprised both vaccinated and unvaccinated persons. The highest convalescent mean titer and the largest incremental increase in mean titer among the unvaccinated were observed against the Oti strain but threefold rises also occurred against both the PR8 and the 1947 Rhodes strain (Table II). A definite rise to Swine 1976 strain also took place. In the vaccinated group, there was also an increase in titer against all strains used, although the incremental rises were greatest against the Oti and Rhodes strains.

TABLE IV.
Cross Hemagglutination-Inhibition and Mouse Neutralization Tests with Allantoic Fluid Antigens and Specific Ferret Antisera.

Ferret sera	Serum stage	Virus strains									
		PR8 F7M593E69		Rhodes F4M7E23		FM1 M37E15		Oti M179E33		Swine 1976 M38E19	
		HI	MN	HI	MN	HI	MN	HI	MN	HI	MN
G28	N	<32	<4	<32	—	—	—	<32	—	<32	—
PR8-F105	I	4096	1024	<32	24	—	—	<32	<4	<32	<4
G12	N	<32	—	32	—	<32	—	<32	—	<32	—
PR8-F105	I	1024	—	32	—	<32	—	<32	—	<32	—
K24	N	<32	—	<32	<4	—	—	<32	—	<32	—
Rho-F4M7E12	I	<32	4	2048	512	—	—	<32	<4	<32	<4
K25	N	<32	—	<32	—	<32	—	<32	—	<32	—
Rho-F4M7E12	I	<32	—	2048	—	128	—	<32	—	<32	—
K46	N	<32	—	<32	—	<32	—	<32	—	<32	—
FM1-M37E14	I	<32	—	2048	—	1024	—	<32	—	<32	—
K31	N	<32	—	<32	—	—	—	<32	<4	<32	—
Oti-M179E33	I	128	128	128	128	—	—	2048	512	32	<4
K30	N	<32	—	<32	—	<32	—	<32	—	<32	—
Oti-M179E33	I	128	—	128	—	<32	—	2048	—	<32	—
K37	N	<32	—	—	—	—	—	<32	—	<32	<4
Swine 1976-M52	I	<32	<4	—	4	—	—	<32	<4	512	1280
K38	N	<32	—	32	—	32	—	<32	—	<32	—
Swine 1976-M52	I	<32	—	64	—	32	—	<32	—	256	—

F = Ferret. M = Mouse. E = Chick embryo.
Numbers after letters correspond to number of passages in animals.
N = Normal serum. I = Immune serum.
All titers are reciprocals of one.
— = Not done. HI = Hemagglutination-inhibition titer. MN = Neutralization titer in mice.

In this respect the response of the children appeared to be clearly more specific.

A further comparison of the response of the children and the adults to the A-prime infection is listed in Table III as the per cent showing incremental change in titer. This demonstrated again greater specificity on the part of the children with a rather striking parallel in the pattern of response to the Rhodes and Oti strains. The results in the adult group were less pronounced but followed the same pattern. As previously noted vaccination tends to mask the effect of A-prime infection on the antibody responses to the PR8 strain.

It appears that the Oti strain, when tested against human sera from individuals who had experienced A-prime infection, showed antibody reactions which strongly suggest that it is an A-prime strain.

Results of Studies Using Specific Animal Antisera. The results in the two illness groups indicated the desirability of further investigation of the immunological characteristics of the Oti strain. Table IV shows the relation of cross-inhibition tests using specific ferret antisera against Type A, A-prime and swine strains. It is readily apparent that the Oti strain is more closely related to the A-prime and A strains than to the Swine 1976 strain. Furthermore, neutralization tests in mice paralleled the agglutination-inhibition tests. Animals inoculated with the Oti strain developed high antibody titers against the Oti strain and slightly less antibody against the Type A or A-prime strains while exhibiting no antibody against the swine strain. Animals inoculated with the A and A-prime strains had no antibody against either the Oti or the swine strain 1976. These results

differed from the findings in man where experience with an A-prime infection caused rises in anti-Oti antibody. Using the more specific animal sera less evidence of cross inhibition between the Oti and other strains was obtained than between the A-prime strains of Rhodes and FMl. The Oti strain did not crossreact with the antisera to the PR8, Type A, strain. It should be pointed out, however, that anti-Oti serum gave as much inhibition of the Rhodes strain as anti-Rhodes serum did with the FMl strain. Further, there is considerable variation in the amount of cross reaction obtainable with strains of the A-prime group. In any event, it appears that this strain behaves like a type A strain and certainly does not have the characteristics of the swine strains described by Shope.[10] These data, while not decisive, taken together with the results obtained with human sera seem to warrant the inclusion of the Oti strain with the A-prime groups of 1947.

Discussion. The history of the Oti strain seems sufficiently accurate to accept the fact that it was originally isolated from infected swine in Korea where swine influenza is recognized largely as a low grade endemic disease and differs from the sharp epidemics described in the United States. The data presented in this paper call attention to the definite antigenic resemblance of this swine strain, isolated in 1939, to strains such as the A-prime group first prominently encountered in human disease in 1947. It may be that some of the peculiarities of that group of strains are related to their earlier adaptation in the animal host. If subsequent studies should increase the possibility that these infections of man arose from a swine host, it would represent a reversal of the sequence of host infection from that suggested earlier, by Koen[9] and Shope[10] for swine influenza recognized in the United States. On the other hand, the virus may have been of human origin, fortuitously detected in swine.

Conclusions. 1. A strain of swine influenza virus (Oti), isolated in 1939, has been reinvestigated by serological means and found antigenically to resemble some members of the human A-prime influenza virus group.

2. Significant increases in the levels of antibody against this swine strain of influenza virus were detected in the convalescent blood specimens of children who had had experience during the A-prime influenza epidemic of early 1947. High titers of antibody were also found against the current A-prime strains.

3. Adults involved in the same epidemic also showed significant antibody increases against the same swine strain and the current A-prime and Type A strains.

4. Results of cross hemagglutination inhibition tests with specific ferret anti-sera supported the observations made from the serological tests with human sera.

5. The relationship of this swine strain to members of the A-prime group has been discussed.

[9] Dorset, M., McBryde, C. N., and Niles, W. B., *J. Am. Vet. Assn.*, 1922-23, **62**, 162.

[10] Shope, R. E., *Harvey Lectures*, 1935-36, **31**, 183.

Received April 25, 1949. P.S.E.B.M., 1949, **71**.

17140. The Hyperglycemic Action of Some Analogs of Epinephrine

EVAN W. MCCHESNEY, JOHN P. MCAULIFF, AND HAROLD BLUMBERG.*
From the Sterling-Winthrop Research Institute, Rensselaer, N. Y.

The preparation in the chemical laboratories of this Institute of a series of compounds to be studied for bronchodilator action has made available to us a group of epinephrine analogs, all of which have this action to a desirable degree. They also lack some of the

* Present address: Endo Products Inc., Richmond Hill, N. Y.