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STUDIES ON THE EFFICACY OF A COMPLEX VACCINE AGAINST INFLUENZA A [1]

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Experimental vaccines containing influenza A virus (*1*) have been tested in human volunteers previously. Stokes and his coworkers (*2*, *3*) gave parenteral injections of active influenza A virus, which had been propagated either in tissue culture medium or in mouse lungs. Subsequently they studied the incidence of acute respiratory disease during epidemics which they considered to be influenza and which affected both the vaccinated and control groups. These authors suggested that the vaccines used had increased immunity to influenza since they found that the attack rate for "febrile respiratory disease" was significantly reduced among the vaccinated individuals. Smith, Andrewes, and Stuart-Harris (*4*), as well as Taylor and Dreguss (*5*), gave subcutaneous injections of formaldehyde-inactivated mouse lung virus to volunteers. They also followed the groups of vaccinated and control individuals through epidemics of influenza which occurred shortly after the vaccine had been administered. Both of these groups of investigators showed that a considerable proportion of the cases they studied had been infected by influenza A virus. However, neither group obtained any evidence that the vaccine used produced demonstrable immunity to the disease. It appears from the available published data that no vaccine has yet been found which will regularly produce immunity to influenza in human beings.

It was recently reported (*6*) that a complex vaccine prepared from chick embryos inoculated with both influenza A virus and the X strain of canine distemper virus was more effective than other vaccines studied in stimulating the production of specific neutralizing antibodies against influenza A virus in human beings. These results made it seem possible that this vaccine might prove somewhat more effective as a prophylactic agent against influenza A than other types of vaccines investigated previously. To test this possibility, field tests with the complex vaccine were carried out in order that

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any active immunity which followed its administration could be assessed directly under naturally occurring conditions. It is the purpose of this paper to report the results obtained and to present evidence that, after a single subcutaneous injection of the complex vaccine given 4 months prior to an epidemic of influenza, there occurred a significant reduction in the incidence of influenza A among vaccinated individuals.

METHODS

Viruses.—The PR8 strain (*7*) of influenza A virus (*1*) and the X strain (*8*) of canine distemper virus were used in this study.

Vaccine.—The preparation of the complex chick embryo vaccine has been described in detai previously (*6*). Eight separate lots of vaccine were used in this study. The method of preparation of these lots was, briefly, as follows: A 1 percent suspension of the ninth chick embryo passage of the PR8 strain of influenza A virus was mixed with a 10 percent suspension of the second, third, or fifth chick embryo passage o the X strain of canine distemper virus. The mixture was inoculated onto the chorio-allantoic membrane of 9- to 12-day-old white Leghorn chick embryos. The embryos were incubated for an additional 6 days, after which they were removed from their shells aseptically and ground to a 33 percent suspension in 0.85 percent NaCl. Sufficient formalin was added to give a final concentration of formaldehyde of 1:4,400, and the suspension was stored at 4° C. for 48 hours. Then sufficient 0.85 percent NaCl was added to make a final suspension of 20 percent ch ck embryo, and the excess formaldehyde was neutralized by the addition o ammonia water to a final concentration of ammonia of 1:16,000. The suspension was then centrifuged for 15 minutes at 1,500 r. p. m. The supernatant was removed, distributed in pyrex ampoules, frozen in a mixture of alcohol and solid CO_2, and desiccated by the method of Bauer and Pickels (*9*). The desiccated vaccine was stored at 4° C. and subsequently was kept at room temperature for varying intervals.

Seven of the eight lots of vaccine contained by mouse titration similar quantities of influenza A virus before formaldehyde inactivation. On the average, 1 cc. of each of these seven lots contained $10^{4.6}$ fifty percent mortality doses and $10^{6.4}$ mouse pneumonia doses (*6*) of influenza A virus. The remaining lot of vaccine, designated Lot 4, contained only $10^{3.3}$ and $10^{5.1}$ corresponding doses of influenza A virus before inactivation. Prior to its administration Lot 4 was kept at room temperature for a period of 55 days.

Immediately before the vaccine was administered, the ampoule was opened and the dry powder rehydrated by the addition of a quantity of sterile distilled water equal to the original liquid volume. Each volunteer was given a single injection of 1 cc. of the vaccine subcu-

taneously. This quantity contained, on the average, approximately 20 mg. of chick embryo protein.

Volunteers.—In a number of State institutions volunteers were selected at random from among the inmate population. Approximately 40 percent of the inmates were vaccinated; the proportion ranged from 35 to 60 percent in single institutions. The remaining inmates in the same institutions who had not been vaccinated were considered to be normal controls.

Serum.—Serum was obtained from a number of volunteers who received each lot of vaccine. Two serum specimens were taken from each of these individuals, one immediately before vaccination and another 2 weeks later. From some individuals serum was also obtained 4 months after vaccination. When the epidemic of influenza occurred serum was obtained from as many cases as possible in both the vaccinated and control groups. Two serum specimens were taken from each case, one during the acute phase of the disease and another between 2 and 4 weeks later during convalescence.

Neutralization tests.—The technique by which neutralization tests were carried out has been described previously (*10*) and additional pertinent details are given in the preceding paper (*11*).

Calculation of neutralizing capacity.—The method by which this constant was calculated for each serum tested has been reported in earlier communications (*11*, *12*).

Complement fixation tests.—The technique used in the complement fixation tests was identical with that described by Eaton and Rickard (*13*).

Determination of etiology of influenza.—Acute-phase and convalescent sera from individual cases were tested simultaneously. In each case studied the titers of complement-fixing antibodies against influenza A virus of both serum specimens were determined. An increase of one dilution or more in the titer of the convalescent serum was considered a significant increase in antibodies and was, therefore, taken as evidence that the patient had influenza A. In approximately 30 percent of the cases studied the neutralizing capacities against influenza A virus of both serum specimens were determined also. An increase in neutralizing capacity during convalescence of log 0.86 was considered a significant increase in antibodies which indicated that influenza A had occurred. In those cases in which there was a discrepancy between the results of the complement fixation and the neutralization tests, the former tests were disregarded and an etiological diagnosis was determined by the latter tests since these were considered to be the more accurate. In selected cases throat washings were tested in ferrets, hamsters, or both, for the presence of influenza A virus by the techniques described in a preceding paper (*14*).

EXPERIMENTAL

Neutralizing antibodies against influenza A virus before and after vaccination.—The neutralizing capacities against the PR8 strain of influenza A virus of serum obtained from a number of volunteers immediately before and at intervals after the subcutaneous administration of 1 cc. of complex vaccine were determined. It was found that, except for Lot 4, the various preparations of vaccine used were of approximately equal antigenic potency, as judged by the increase in neutralizing antibodies which followed their administration in individuals with comparable prevaccination antibody levels.

The results are presented graphically in figure 1. Individuals who were given Lot 4 have been excluded from this analysis for reasons

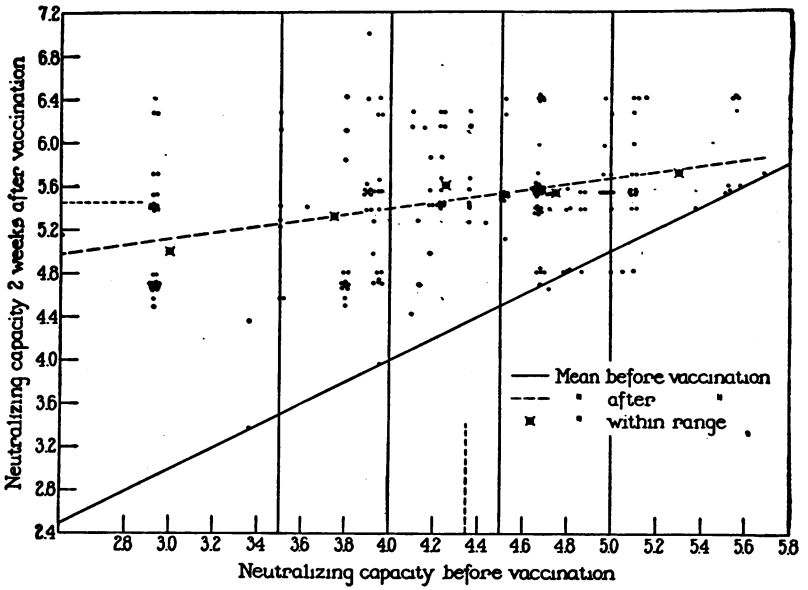

FIGURE 1.—Neutralizing antibody levels against influenza A virus in the serum of 288 individuals before and 2 weeks after each had received one subcutaneous injection of 1.0 cc. of complex vaccine.

given below. The neutralizing capacity of the prevaccination serum has been plotted against the neutralizing capacity of the serum taken 2 weeks after vaccination. A straight line has been drawn through those points which correspond to identical capacities before and after vaccination. The vertical distance from this line to a point above it represents the extent of the increase in antibody level observed in an individual volunteer. It will be noted that among 288 vaccinated individuals an increase in neutralizing antibodies was demonstrated in all but 17 instances. It is apparent that there were wide differences in the quantities of antibodies produced, even by individuals who possessed identical antibody levels prior to vaccination. The wide variations in the specific responses to the vaccine seemed to be almost independent of the initial antibody level. However, the increase in

neutralizing capacity was related to the prevaccination level. In general, the lower the neutralizing capacity before vaccination, the greater was the increase in antibodies after vaccination. The geometric means of the neutralizing capacities of the postvaccination sera obtained from individuals who initially possessed serum in the neutralizing capacity ranges, log 3.50 or less, log 3.51 to 4.00, log 4.01 to 4.50, log 4.51 to 5.00, and log 5.01 to 5.80, respectively, were calculated and are shown in figure 1. A straight broken line which appeared to fit these five points was drawn through them. It will be observed that this line has a definite slope and that the mean neutralizing capacity following vaccination was highest in the group who possessed before vaccination the highest antibody level, even though the mean *increase* in neutralizing capacity in this group was lowest of all. The mean postvaccination neutralizing capacity for the entire group was log 5.45. Among 114 individuals who possessed, prior to vaccination, capacities in the range log 4.35 or less, the mean increase after vaccination was log 1.70, which represents an increase in antibody level of 50 times. This figure corresponds fairly well with that obtained previously (*6*) in a smaller group in the same range. Among 35 individuals in this antibody range who received Lot 4 the mean increase in neutralizing capacity after vaccination was only log 0.69, which represents an increase in antibody level of but 5 times. For reasons which are not clear, Lot 4 appears to have been of very low antigenic potency, and the antibody responses which followed its administration were much lower than those observed with any of the other lots used.

In figure 2 are shown graphically the relative distributions of antibody levels against influenza A virus among 1,321 normal persons, 288 individuals 2 weeks after vaccination, and 78 individuals 4 months after vaccination. The proportion of individuals in each of the neutralizing capacity ranges 0 to log 2.62, log 2.63 to 3.49, log 3.50 to 4.35, log 4.36 to 5.22, and log 5.23 to 6.09, respectively, have been plotted against the mean capacities in each range. Smooth curves have been drawn through the points to facilitate an interpretation of the results. The data for normal individuals are identical with those given in the preceding paper (*11*). It will be observed that the proportion of individuals in the two highest ranges was markedly increased 2 weeks after vaccination and that less than 1 percent of vaccinated individuals had neutralizing capacities of log 4.0 or less at this time. Four months after vaccination there was a definite reduction in the proportion of individuals in the two highest ranges, but no individuals were encountered at this time with neutralizing capacities of log 3.5 or less. The change in the distribution of antibodies from that found among normal individuals 2 weeks and 4 months after vaccination is clearly shown.

In a previous paper (*11*) it was shown that there was a correlation between neutralizing antibody levels against influenza A virus and the occurrence of influenza A. It was found that the higher the level of antibodies, the less likely was the development of the disease. It has been of interest to compare the distribution of antibody levels among cases of influenza A with that of individuals vaccinated 4 months previously. In figure 3 these data are presented graphically. The frequency with which the various neutralizing capacity ranges were encountered in 310 cases of influenza A and among 78 vaccinated individuals has been plotted against the mean capacity in each range. Smooth curves have been drawn through the experimental points. A vertical line has been inserted in the graph at a point corresponding

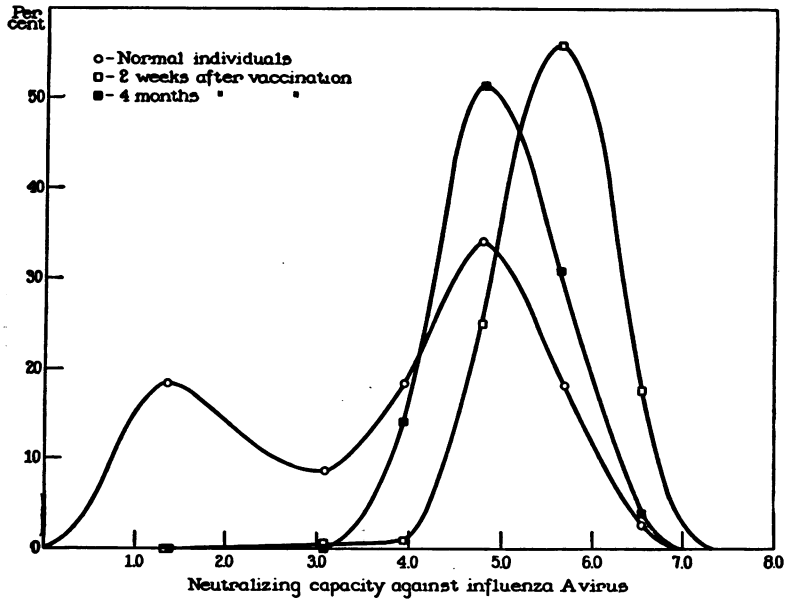

FIGURE 2.—Distribution of neutralizing antibody levels against influenza A virus among 1,321 normal persons, 288 individuals 2 weeks after vaccination, and 78 individuals 4 months after vaccination. Each vaccinated person was given one subcutaneous injection of 1.0 cc. of complex vaccine.

to the neutralizing capacity log 3.50. It was found that no vaccinated individual tested had a capacity of less than log 3.50 at the end of 4 months. On the other hand, as was shown previously (*11*), 41 percent of cases of influenza A occurred in individuals with antibody levels lower than log 3.50. If it can be assumed that the neutralizing antibodies which were produced as a result of vaccination were of identical significance to those naturally present, it can be calculated, on the basis of these data, that the incidence of influenza A among vaccinated individuals should have been reduced by approximately 30 percent.

Incidence of influenza A among vaccinated and control groups.— During October 1940 groups of volunteers in 15 institutions in Florida

and Alabama were given complex vaccine against influenza A. The total population of these institutions was 17,595. Of this number 7,907 persons were given a single subcutaneous injection of vaccine. The remaining 9,688 individuals were not vaccinated and were considered as normal controls.

Approximately 4 months after the vaccine had been given, epidemics of influenza occurred in 10 institutions. In 4 of these institutions Lot 4 had been used, while in the remaining 6 institutions other lots of vaccine had been given. It will be recalled that Lot 4 was of very low antigenic potency and that it produced only a small antibody response, whereas the other lots of vaccine stimulated the formation of considerable quantities of neutralizing antibodies against influenza A virus.

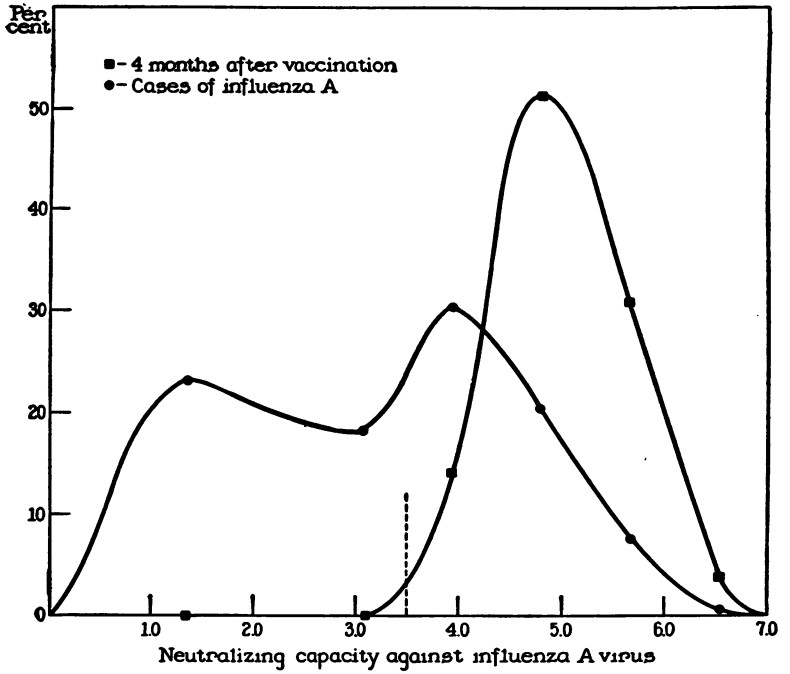

FIGURE 3.—Distribution of neutralizing antibody levels against influenza A virus among 310 cases of influenza A and 78 individuals 4 months after vaccination. Each vaccinated person was given one subcutaneous injection of 1.0 cc. of complex vaccine.

All cases of influenza which occurred in either the vaccinated or the control groups were recorded. Acute-phase and convalescent sera were obtained from as many cases as possible in both groups. These sera were tested by the methods described above in order that an etiological diagnosis could be established in each instance.

It was obviously impractical to attempt to carry out neutralization tests against influenza A virus with two serum specimens obtained from each case since the number of mice required would have been extremely large. However, before it was possible to place reliance upon the results of complement fixation tests with serum from vacci-

nated individuals; it was necessary to compare the results obtained by complement fixation and by neutralization techniques in a number of cases.

The results of both tests on acute-phase and convalescent sera from 282 cases are shown in table 1. It will be observed that among 156 cases in the control groups the two tests gave similar results in 85.9 percent and divergent results in 14.1 percent of cases. Among 126 cases in vaccinated individuals the two tests gave similar results in 80.2 percent and divergent results in 19.8 percent of cases. In the cases in the control groups the complement fixation test showed a significant increase in antibodies in 90.7 percent as many cases as did the neutralization test. In the cases among vaccinated individuals, on the other hand, the complement fixation test revealed a significant increase in antibodies in 103.8 percent as many cases as did the neutralization test. The results seemed sufficiently similar to make it feasible to use the complement fixation technique in establishing an etiological diagnosis. Despite the rather large error introduced by this method, it seemed probable, on the basis of comparisons between the two tests, that the complement fixation test would tend to increase rather than decrease the actual number of cases of influenza A among vaccinated individuals.

TABLE 1.—*Comparison between results of neutralization tests and complement fixation tests on acute-phase and convalescent sera from cases of influenza among vaccinated and control individuals*

Test which showed a significant increase in antibodies against influenza A virus	Cases of influenza			
	Control group		Vaccinated group (4 months after vaccination)	
	Number	*Percent*	*Number*	*Percent*
Neutralization and complement fixation	113	72.4	67	53.2
Neutralization only	17	10.9	11	8.7
Complement fixation only	5	3.2	14	11.1
Neither test	21	13.5	34	27.0
Total	156	100.0	126	100.0
Total discrepancies between tests	22	14.1	25	19.8
Influenza A by neutralization test	130	100.0	78	100.0
Influenza A by complement fixation test	118	90.7	81	103.8

In the 10 institutions there was a total of 1,450 cases of influenza. It was possible to establish an etiological diagnosis in 967 cases, or 66.7 percent. In the remaining cases either one or both serum specimens were unavailable. The results obtained in each institution are shown in table 2. Because Lot 4 was found to have stimulated the production of only about one-tenth as much antibodies as other lots of vaccine used, the results in Institutions 1 to 4, in which Lot 4 had been given, have been separated from those in the other institutions. It will be observed that the attack rate for clinical influenza among the control groups varied from 3.8 percent in Institution 8 to 36.1

percent in Institution 2. The attack rate for clinical influenza was lower in the vaccinated groups than in the control groups in Institutions 1 and 3 and higher in Institutions 2 and 4. When the 4 institutions were considered collectively, it was found that clinical influenza occurred in 11.4 percent of control individuals and in 9.3 percent of vaccinated individuals.

TABLE 2.—*Incidence of influenza among vaccinated and control groups in 10 institutional outbreaks 4 months after vaccination*

Institution	Control group							Vaccinated group							Influenza A ratio V/C
	Number	Cases of influenza		Cases studied		Incidence		Number	Cases of influenza		Cases studied		Incidence		
				Influenza A	Influenza "Y"	Influenza A	Influenza "Y"				Influenza A	Influenza "Y"	Influenza A	Influenza "Y"	
		No.	*Pct.*	*No.*	*No.*	*Pct.*	*Pct.*		*No.*	*Pct.*	*No.*	*No.*	*Pct.*	*Pct.*	
1	750	57	7.6	28	14	5.1	2.5	1,000	68	6.8	29	13	4.7	2.1	0.88
2	277	100	36.1	32	12	26.4	9.7	160	73	45.6	20	7	33.8	11.8	1.28
3	2,700	254	9.4	79	60	5.3	4.1	1,900	134	7.1	41	29	4.1	3.0	.77
4	1,425	175	12.3	122	26	10.2	2.1	225	31	13.8	22	2	12.4	1.4	1.21
Total	5,152	586	11.4	261	112	7.9	3.5	3,285	306	9.3	112	51	6.4	2.9	.81
5	648	87	13.4	77	7	12.3	1.1	210	18	8.6	14	3	7.1	1.5	.58
6	190	46	24.2	25	2	22.0	2.2	110	36	32.8	9	5	21.0	11.8	.95
7	2,150	157	7.3	86	39	4.9	2.4	1,850	98	5.3	43	30	3.1	2.2	.63
8	875	33	3.8	16	8	2.5	1.3	725	20	2.8	8	7	1.4	1.4	.56
9	140	26	18.6	16	3	15.7	2.9	160	12	7.5	6	4	4.4	3.1	.28
10	400	16	4.0	8	7	2.0	2.0	400	9	2.2	1	7	.2	2.0	.10
Total	4,403	365	8.3	228	66	6.6	1.7	3,455	193	5.6	81	56	3.3	2.3	.50

In Institutions 5 to 10 the attack rate for clinical influenza was lower in the vaccinated groups than in the control groups in all except Institution 6. Considered collectively, clinical influenza occurred in 8.3 percent of control individuals and in 5.6 percent of vaccinated individuals in Institutions 5 to 10.

Since on the average 66.7 percent of cases were studied in order that an etiological diagnosis could be established, it is possible to calculate with reasonable accuracy the proportion of cases of influenza A in both groups in each institution. In table 2 the number of cases studied, the number in which a significant increase in antibodies against influenza A virus was demonstrated, and the number in which no significant increase in antibodies could be demonstrated are shown. On the basis of the proportion of cases studied which showed evidence of an antibody response against influenza A virus, the probable number of cases of influenza A among the total cases of clinical influenza in a given group could be calculated. From this figure the probable incidence of influenza A in a given group was determined. In a similar manner, on the basis of the proportion of cases which did not show evidence of an antibody response against influenza A virus, the probable

incidence of influenza of unknown cause, or influenza "Y" (*14*) in a given group was determined.

It will be seen that the incidence of influenza A varied from 2.0 percent to 26.4 percent in the control groups and from 0.2 percent to 33.8 percent in the vaccinated groups in Institutions 10 and 2, respectively. The incidence of influenza A was lower in the vaccinated groups than in the control groups in Institutions 1 and 3 and higher in Institutions 2 and 4. Taken together influenza A occurred in 7.9 percent of control individuals and in 6.4 percent of vaccinated individuals in Institutions 1 to 4. In Institutions 5 to 10 the incidence of influenza A was lower in the vaccinated groups than in the control groups in all instances. Considered as a whole, influenza A occurred in 6.6 percent of control individuals and in 3.3 percent of vaccinated individuals in these 6 institutions. It should be noted that with the single exception of Institution 6, the incidence of influenza "Y" in the control groups was almost identical to that in the vaccinated groups in each institution.

The V/C ratios shown in table 2 express in a single figure the difference between the incidence of influenza A in the vaccinated and control groups in each institution. This ratio was calculated by dividing the incidence of influenza A among vaccinated individuals by the incidence of influenza A among control individuals. A V/C ratio of 1.0 would indicate that the incidence was identical in the two groups. Ratios of less than 1.0 indicate the extent to which the incidence of influenza A was lower among vaccinated individuals. It will be noted that in Institutions 1 to 4 the ratio varied from 0.77 to 1.28 and that when the groups were considered collectively, the ratio was 0.81. This indicates that in these institutions there were 19 percent fewer cases of influenza A among the vaccinated group than among a control group of the same size. In Institutions 5 to 10 the ratio varied from 0.95 to 0.10 and for all 6 institutions it was 0.50. This indicates that in these institutions there were 50 percent fewer cases of influenza A among the vaccinated group than in a control group of identical size.

DISCUSSION

Influenza A is only one etiological variety of the clinical syndrome termed influenza. It is now well established that there are other distinct etiological varieties of influenza and that these specific diseases may and often do occur in epidemics of influenza simultaneously with influenza A.

The vaccine which was used in this study contained inactivated influenza A virus and stimulated the production of antibodies against this agent. It did not contain influenza B virus and it was to be expected, therefore, that the vaccine would not produce an antibody

response against this virus. This has been found to be the case, and the additional antibodies which were produced following the administration of the vaccine were directed merely against influenza A virus.

Because of the constituents of the vaccine it was anticipated that any increased immunity which might have resulted from its administration would be operative only against influenza A and not against influenza B or influenza of unknown cause. To determine what efficacy the vaccine had in increasing immunity to this disease, it was necessary to establish the etiology of the epidemic which affected the vaccinated and control groups under study. To accomplish this it seemed essential to determine the nature of the agent responsible for the infection in as many cases as possible in both groups. Only by these extensive investigations did it seem feasible to arrive at an accurate appraisal of the possible prophylactic effectiveness of the vaccine against influenza A.

The results of these studies indicate that a single subcutaneous injection of complex vaccine given 4 months before the occurrence of an epidemic of influenza significantly reduced the incidence of influenza A in the vaccinated groups. The extent to which the incidence of influenza A was reduced seems to have been related to the extent to which antibodies against influenza A virus were increased. It will be recalled that among volunteers who were given a lot of vaccine one-tenth as effective as other lots in stimulating the production of antibodies, the incidence of influenza A was only 19 percent lower than among comparable control individuals. However, among volunteers who were given lots of vaccine which resulted in a considerable increase in antibodies, the incidence of influenza A was only one-half the incidence of the disease among comparable control individuals.

These results tend to confirm what might have been expected from what has been demonstrated previously (*11*) concerning the relationship between antibody levels against influenza A virus and the occurrence of influenza A. If the antibodies which resulted from the administration of vaccine had the same significance as antibodies normally present in human serum, it should be possible to calculate the extent to which antibody levels increased after vaccination would decrease the incidence of the disease. Calculations of this kind were carried out, and it was found that the observed reduction in the incidence of influenza A among vaccinated individuals was, if anything, somewhat greater than that anticipated on the basis of the increased antibody levels which were present 4 months after vaccination. It appears, therefore, that specific antibodies produced after vaccination have at least equal significance, but probably no greater significance, in contributing to immunity to influenza A than those possessed by normal individuals.

It seems important to emphasize that the available evidence indicates that no level of antibodies possessed by normal individuals, even though some were very high, could be taken to indicate complete immunity to influenza A. It has been shown (*11*) that in individuals with high antibody levels the disease occurred with markedly reduced frequency but still did occur occasionally. Similar considerations seem applicable to the degree of immunity which was present 4 months after the administration of the vaccine. The incidence of influenza A was significantly reduced, but the disease was not entirely prevented in vaccinated individuals.

The results obtained indicate that a vaccine which significantly increased antibodies against influenza A virus also significantly reduced the incidence of influenza A. Since the vaccine contained inactivated virus, it seems probable that its action was comparable to that of an inert antigen and that it served only to stimulate the production of antibodies and did not alter other factors which may possibly contribute to a state of relative immunity to influenza A. Under these circumstances it is likely that the increased immunity observed was directly attributable to the increased antibody levels possessed by vaccinated individuals.

The fact that influenza of unknown cause was not significantly reduced among vaccinated individuals is additional evidence for the specific relationship between antibody levels against one influenza virus and the probability of the occurrence of infection by the homologous virus.

SUMMARY

In volunteers who had received a single subcutaneous injection of complex vaccine of good antigenic potency 4 months previously the incidence of influenza A during an epidemic was 50 percent lower than among unvaccinated individuals in identical environmental circumstances. The incidence of influenza of unknown cause was not significantly different in the two groups.

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PRESENT-DAY METHODS FOR CONTROLLING *AËDES AEGYPTI* MOSQUITOES [1]

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Although the circular of the United States Public Health and Marine Hospital Service entitled "Yellow Fever and Mosquitoes" (*1*), issued during the last invasion of yellow fever, the 1905 New Orleans epidemic, contained information on mosquito-control measures that remains basic, experience and studies have resulted in still more specific knowledge about the habits and the breeding places of the yellow fever mosquito, *Aëdes aegypti*.

Since this species of mosquito breeds only in artificial containers it is controlled simply by frequent careful inspections of *all* artificial containers around premises and the application of control methods in the area to be sanitated. Wherever possible water-holding containers are destroyed; those that serve indispensable purposes are treated. This is a simple formula, and no complicated rules are necessary to apply it. But in a modern community it is very difficult to ferret out and to destroy or treat all water-holding containers.

This paper attempts to explain present-day methods used or developed by the Aëdes Aegypti Control Unit established by the Public Health Service, of which the writer was for 2 years the officer in charge.

All inspectors and supervisory personnel must be trained so that they can perform their tasks efficiently. Time in training inspectors may be saved by assembling them and projecting onto a screen slides showing the typical places where *aegypti* larvae are found. The modern camera with high-speed lens and fast film has made it easy to obtain a collection of such pictures.

Assignments of house-to-house inspectors are made daily from a city map divided into districts and sections. The results of a few days of actual inspections disclose whether the subdivisions made on the map should be changed.

[1] Presented before the National Malaria Committee, Louisville, Ky., November 13–15, 1940.

The cycle of house-to-house inspections should be about 7 days in summer. This can be increased to 14 days as the *Aëdes aegypti* index approaches zero. This index was used by us to observe the progress made in reducing the infestation of the aquatic forms of *aegypti* in the area in which the work was being done. It is the percentage of premises inspected where larvae were found expressed as a whole number multiplied by the percentage of samples collected containing *aegypti* larvae. The first-mentioned percentage expressed as a whole number shows the index of "domestic" mosquitoes, and multiplying it by the percentage of samples collected containing *aegypti* larvae is an attempt to produce a figure that will indicate the *aegypti* infestation. One sample of larvae was collected by the house-to-house inspectors from every property where larvae of "domestic" mosquitoes were found. An entomologist identified the specimens collected (*2*).

The house-to-house inspector must find all containers sustaining the aquatic forms of the *aegypti* mosquito and render harmless as many of these containers as he can. A record of the number of artificial containers producing *aegypti* is very necessary. A record of the number of water-holding containers that could produce mosquitoes has value because it gives an idea of the junk and debris that may be in the householders' yards.

In all sections of the municipality the house-to-house inspectors will find water-holding containers that cannot be destroyed or emptied because of their use. These can be controlled by placing them on a list to be visited every 10 days or oftener by a "10-day" inspector. Whenever possible this inspector applies light Diesel engine fuel oil to the water surface, using hand operated compressed air spray guns. It has been difficult to find spray guns equipped with oil-resisting hose and gaskets, but such equipment is now available. It is well worth while to purchase hose and gasket replacements that are oil resisting.

In order to control production in catch basins it is necessary to apply oil to every wet catch basin at least once every 10 days. Experience has shown that successful catch basin oiling requires the inspector to stop long enough at every catch basin to apply a sufficient dose of the oil larvicide. Inspectors should not be required to cover too large a territory in a given time. Many catch basins contain so much floating debris that it is likely that an oil spray applied through the surface grating will not cover the water surface and mosquito production will not be stopped by the oil application.

It was our experience that better results could be obtained in such catch basins by having the inspector submerge the oil pipe below the floating debris before applying the dose of larvicide.

Catch basin breeding can be controlled by applying oil from a pressure tank carried on a motorcycle or a light truck. A hose, quick operating valve, and an extension spray nozzle are necessary. While

it is usually possible to obtain compressed air from gasoline filling stations, a more dependable source of air is an automatically controlled gasoline-operated air compressor carried on the truck.

Old cisterns should be filled in whenever their owners can be induced to do so. In some cities there still is no public water supply and the citizens have to depend upon the storage of rainwater in underground cisterns or in surface tanks. Property owners are shown how cisterns, tanks, rain barrels, and other such containers can be reconstructed to render them mosquito-proof. When owners suggest screening openings and barrel tops the proper kind of durable 18-mesh wire cloth is recommended to them. Mosquito-proof construction is an important part of a control program but owners often are financially unable to make such improvements and other methods are needed to control mosquito production.

Because top-feeding minnows had been used successfully in open containers in yellow fever control in Tampico, Mexico, (*3*) and Guayaquil, Ecuador, (*4*) experiments were made by us to determine whether these minnows would feed in the dark. Experiments of others had shown that *Gambusia holbrooki* minnows feed mainly by attacking food when it is in motion, and it had been concluded that they were unsuited for introduction into dark, covered cisterns. Our experiments in Key West, Fla., (*2*) showed that their ability "to eat mosquito larvae seemed to depend more upon their appetite or capacity than upon the amount of light present," and that they were the local fish best suited to this purpose.

Cisterns were stocked, using one adult fish per square foot of water surface, or, roughly, 50 fish in an average cistern. The same proportion was used for other artificial containers.

Care is necessary in handling these fish, and the pregnant females are even more susceptible than the males to handling and chlorination injuries. Little harm results to either sex when reasonable care is used, and they are able to stand being poured into cisterns or being introduced through small openings when necessary, although some fish are always lost.

Before introducing them into cisterns it is necessary to acclimate them by placing them in successive containers of pond water, a mixture of pond and cistern water, and cistern water.

As a precaution against possible contamination of cisterns, the Key West sanitary officer had subjected *Gambusia* minnows to an overnight chlorinated water bath before placing them in cisterns. This practice was continued by us and experiments plus experience resulted in the use of dosages of liquid hypochlorite that would produce a chlorine residual of 0.1 to 0.15 part per million. The hypochlorite was added carefully because a high concentration, or overcontact with chlorinated water, always causes a high mortality among fish.

Occasionally householders refuse to permit fish to be placed in their cisterns. Such cisterns must be sprayed every 10 days with sufficient kerosene to form an unbroken film of oil on the water surface. Kerosene evaporates quickly and there is but slight possibility of its being drawn up into the water pipes because pump suction pipes extend almost to the bottom of the cistern.

Gambusia minnows are unable to remove heavy larval infestations from cisterns. This condition is met by spraying a cistern first with kerosene to kill the larvae. *Gambusia* are then introduced to prevent reinfestation. Apparently a kerosene film is not harmful to *Gambusia*.

As a means of preventing the development of a yellow fever epidemic in the event a case of this disease should occur, it had been planned to disinsecticize thoroughly the houses in the neighborhood of the first case to be reported. Both a pressure spray gun operated by a portable electrically driven air compressor and a specially built insecticide spraying truck were ready for use. This truck also carried portable electric insecticide sprayers.

This equipment was used in our regular control work to destroy severe infestations of adult *aegypti* mosquitoes inside and under dwellings, garages, and other buildings. The larvicide used was a mixture of 1 part of a concentrated extract of pyrethrum in oil (extract from 20 pounds pyrethrum flowers to each gallon) and 4 parts of light oil (refined kerosene). Householders always welcomed the relief from mosquito annoyance brought about by a disinsectization, although it was often necessary to refuse a request for a disinsectization because an inspection would disclose infestation with insects other than mosquitoes.

The extensive use of automobiles has resulted in the promiscuous discarding of old tires, particularly because of their present slight value as junk. Depending upon the size of the municipality, from hundreds to thousands of rubber tires are discarded weekly. It is almost impossible to remove all of the water accumulating in old tires lying outdoors or once having been outdoors. House-to-house inspectors should advise householders to prevent the accumulation of rainwater in old tires or should direct that they be destroyed. If the regular garbage removal service will not haul them away for incineration, removal becomes an activity of the mosquito control forces.

Junk or second-hand dealers sometimes allow discarded tires to accumulate. If they are not kept dry under cover, they should be piled so that they can be dusted with a paris green-lime mixture. The proportions of the mixture will vary with local conditions. Reinspection of the tires at intervals will show whether or not the application of paris green has been sufficiently heavy. It may be applied with

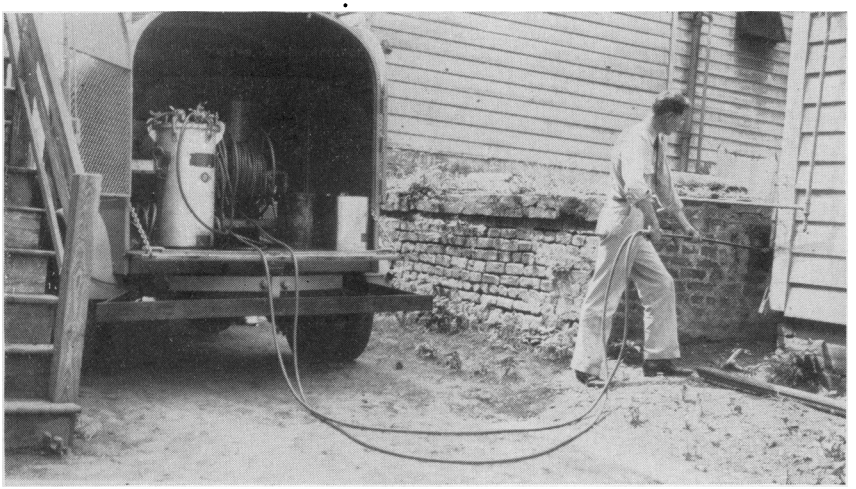

FIGURE 1.—An unused cistern not mosquito-tight being sprayed with kerosene, using a power-driven oil-spraying unit. (This same equipment was used to destroy *Aëdes aegypti* infestations in buildings.)

FIGURE 2.—A "10-day" inspector spraying a cistern with kerosene.

FIGURE 3.—A large pile of old automobile tires in a second-hand yard in which *A. aegypti* are breeding. Production is being controlled by dusting with paris green.

FIGURE 4.—Flashlight pointing to a hidden breeding place, a cistern under the floor of an unoccupied house.

a hand-operated agricultural duster, but a power-driven duster distributes the dust mixture more effectively.

Cemeteries must be included in regular inspections since prolific *aegypti* production is common in flower pots, vases, urns, and the like. It may be controlled effectively by placing in each flower container a pellet made of a wet mixture of 1 part of paris green and 4 parts of plaster of paris. Production in urns and other containers not used for flowers may be controlled by filling them with sand.

In South American cities *Aëdes aegypti* have been regularly controlled and have even been eradicated. Inspectors search the interiors of dwellings, and there are "special service" squads for hunting adult mosquitoes and hidden breeding foci. The search for adult mosquitoes is done chiefly in the interest of securing evidence of the existence of nearby breeding places. Inspectors there can eliminate water plants, plant cuttings, and water-holding containers that are kept indoors. The inspection of interiors of houses in the United States against the wishes of the occupants is something that cannot be attempted under nonepidemic conditions. In this country the inspector is able to inspect the interior of a house only because the occupant already recognizes the value of mosquito control.

Part of the work of the control forces is to secure public cooperation through an educational program presented by trained personnel.

SUMMARY

1. *Aëdes aegypti* mosquitoes are controlled by careful and thorough inspections of all premises, and the elimination of all artificial breeding containers.

2. Inspectors must be trained adequately in order to obtain maximum results.

3. Water-holding containers that cannot be emptied should be oiled regularly or should be stocked with top-feeding minnows.

4. These minnows can be used successfully in dark, covered drinking water cisterns. The minnows should be kept overnight in chlorinated water before being introduced into cisterns.

5. Catch basins require a heavier dose of oil larvicide when they contain floating debris.

6. Houses can be disinsecticized by thorough spraying with pyrethrum in an oil base.

7. Mosquito production in discarded automobile tires can be controlled by dusting them with a paris green-lime mixture.

8. Mosquito production in cemetery flower containers can be controlled by placing paris green pellets in them.

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9. It is impossible under nonepidemic conditions to insist upon indoor inspection of houses, but the public, if properly informed, will cooperate and sometimes will request it.

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THE INFLUENCE OF DIETARY FACTORS UPON THE THERAPEUTIC ACTIVITY OF SULFANILAMIDE IN MICE [1]

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Previous investigation has demonstrated that diet influences the toxicity of sulfanilamide. We found (*1*) that the toxic effects of repeated administration of sulfanilamide to rabbits were greater upon an oats than a cabbage diet. Marshall and Litchfield (*2*) have shown that sulfanilamide administered orally was more toxic to fasting mice than to fed mice, and this difference was related to the concentrations of the drug in the blood. Smith, Lillie, and Stohlman (*3*) have recently shown that the anemia and mortality resulting from repeated oral administration of sulfanilamide to rats could be prevented, to a large degree, by a diet high in protein. Higher concentrations of sulfanilamide in the blood were observed by them in animals on diets low in proteins.

It has been shown that the bacteriostatic action of sulfanilamide in the test tube can be inhibited by peptone (Lockwood and Lynch (*4*)), by extracts of certain plant and animal tissues, and by 4-aminobenzoic acid (Woods (*5*)). Antagonism of the therapeutic effect of sulfanilamide *in vivo* by 4-aminobenzoic acid was demonstrated by Selbie (*6*).

The above considerations led us to investigate the possibility that some normal dietary constituents might influence the therapeutic activity of sulfanilamide.

Experiments were carried out upon a Swiss strain of albino mice. Groups of immature and adult mice were studied. The test organism was a virulent strain of hemolytic streptococcus (Lancefield group A) that we have employed for several years. When passed through mice every 2 to 3 weeks it has maintained a virulence such that 0.5 cc. of an 18-hour culture diluted 10^{-8} is lethal to mice when inocu-

[1] From the Division of Chemotherapy, National Institute of Health.

lated intraperitoneally. Inoculations were made in rotation, taking one animal from each group in succession, to insure uniform exposure for each group under test. Sulfanilamide was injected subcutaneously immediately after inoculation in a 1 percent aqueous solution in all of the experiments. This route was chosen to avoid any variations in gastro-intestinal absorption that might result from dietary changes. At first the mice were kept upon the special diets from 4 to 5 days preceding the therapeutic test until 1 day following the last injection of sulfanilamide when the stock diet of pellets was resumed. Later experiments revealed that the diets should be continued for at least 3 days after cessation of therapy to bring out the maximum influence. The special diets were terminated before the end of the observation period because the animals on the highly deficient diets lost weight and were often in poor condition.

Initial experiments indicated that therapeutic results were better in mice kept on a diet of corn starch (Argo brand) alone than in mice fed upon a diet of pellets employed in our laboratory [2] (table 1).

TABLE 1.—*The influence of dietary factors upon the therapeutic response to sulfanilamide. Mice upon diets for 4 days preceding therapeutic test. Sulfanilamide 0.5 gm. per kilo subcutaneously immediately following streptococcal inoculation, and repeated at daily intervals. Diets continued for 3 days following last dose of drug except in first experiment where diet A was replaced by pellets 24 hours after end of therapy. Composition of diets given in text*

Diet	Number of mice	Mean weight		Mean daily food intake	Streptococcus No. 1685, dilution of culture	Doses of sulfanilamide	Deaths in days										Mortality, percent
		At onset	At inoculation				1	2	3	4	5	6	7	8	9	10	11–14	
		gm.	*gm.*	*gm.*														
A	33		10.8		10^{-6}	3				3	7	4		3				51.5
Pellets	37		13.0			3		15	2	5	5	3	1	1				86.5
A	15	[1]				0	15											100
Pellets	10	[1]				0	9											90
A	24	22.77	21.9	3.0	10^{-5}	3						1	2				1	16.7
E	25	23.3	25.5	3.17		3	2	2		2	1		3	2	1	1	1	60
Pellets	25	22.8	25.8			3	6	3	1	5	4	2						84
Pellets	18	[1]				0	18											100
A	20	17.5	15.07	2.9		2				1			1					10
B	20	17.1	16.6	2.65		2	2			2	5	2	1					60
C	20	17.0	15.47	2.6		2					1					2		15
D	20	16.46	14.2	2.55		2								1	1	1	2	25
E	20	17.35	18.6	3.51		2				2	3		2	1				40
Pellets	4	[1]			10^{-7}	0	3	1										100
	4				10^{-8}	0	2	2										100
	4				10^{-9}	0		1										25

[1] Controls.

[2] These pellets were Hunt Club Dog Chow from the Maritime Milling Co., Buffalo, N. Y. The ingredients, as stated on the bag, were: "Guaranteed analysis, minimum protein 25 percent, minimum fat 3.5 percent, maximum fiber 4 percent; 65 percent protein meat meal, beef liver meal, blood flour, dried skimmed milk, dried cheese whey, cheese rind, soy bean oil meal, wheat flakes, corn flakes, shredded wheat, alfalfa leaf meal, processed wheat bran, 0.5 percent brewers' yeast, 0.05 percent irradiated brewers' yeast, 0.5 percent malt sugar, 3 percent dried kelp, 0.5 percent calcium carbonate (limestone), 0.5 percent bone meal, 0.125 percent charcoal, 0.125 percent salt, 0.00312 percent potassium iodide, 0.25 percent fortified cod liver oil, 0.25 percent shark liver oil, 0.25 percent wheat germ oil."

It was thus indicated that some ingredients of the pellets inhibited the therapeutic action of sulfanilamide. Because of the complex nature of this food, further experiments were undertaken with simplified diets similar to those used by Dr. Smith in his experiments upon rats (*3*).

Experiments were carried out with the following diets:

	A	*B*	*C*	*D*	*E*
Starch	96	78	91	86	63
Casein, purified	0	18	0	0	18
Brewers' yeast, dried [3]	0	0	5	0	5
Cod liver oil	0	0	0	2	2
Olive oil	0	0	0	8	8
Salt mixture [3]	4	4	4	4	4

After a preliminary period of 4 days upon these diets, groups of 20 mice were inoculated intraperitoneally with an 18-hour streptococcus culture. Sulfanilamide, 0.5 gm. per kilo, was administered subcutaneously immediately after inoculation, and repeated in 24 hours. The above diets were replaced by pellets 3 days after the last dose of sulfanilamide. The results (table 1, fig. 1) showed considerably higher mortalities among the animals on diets B and E, containing casein, than among those on the diets of starch plus the other ingredients.

A further comparison was made between the protein-free diet (A), the 21 percent protein diet (E), and the pellet diet containing approximately 25 percent protein. The mortality on diet A was 16.7 percent as compared with 60 percent on diet E and 84 percent on pellets (table 1, figure 2).

Experiments were next carried out in which the amounts of casein and starch were varied. The following diets were employed:

	No. 0	No. 6	No. 18	No. 54
Starch	86	80	68	32
Casein, purified	0	6	18	54
Cod liver oil	2	2	2	2
Olive oil	8	8	8	8
Salt mixture	4	4	4	4

To each 100 gm. of the above diets were added the following vitamins: B_1 0.025 mg., riboflavin 0.1 mg., nicotinic acid 2.5 mg., B_6 0.05 mg., cevitamic acid 2.5 mg.

After a preliminary period of 5 days on the above diets, therapeutic experiments were carried out. The therapeutic activity of sulfanilamide varied inversely with the casein content (table 2). The mice in this experiment were immature, and those on the protein-free diet 0 were in poor condition at the beginning of the therapeutic test. Several died with negative blood and peritoneal smears and

[3] The brewers' yeast contained 60 percent protein. The salt mixture was McCollum's No. 185 (*7*).

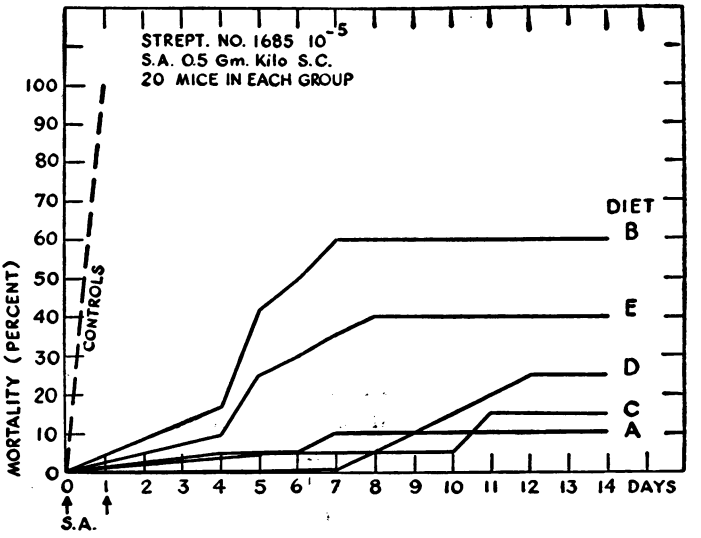

FIGURE 1.—Therapeutic results with sulfanilamide in mice on diet E and on diets consisting of starch plus various ingredients of diet E. The controls received no therapy and were on a pellet diet.

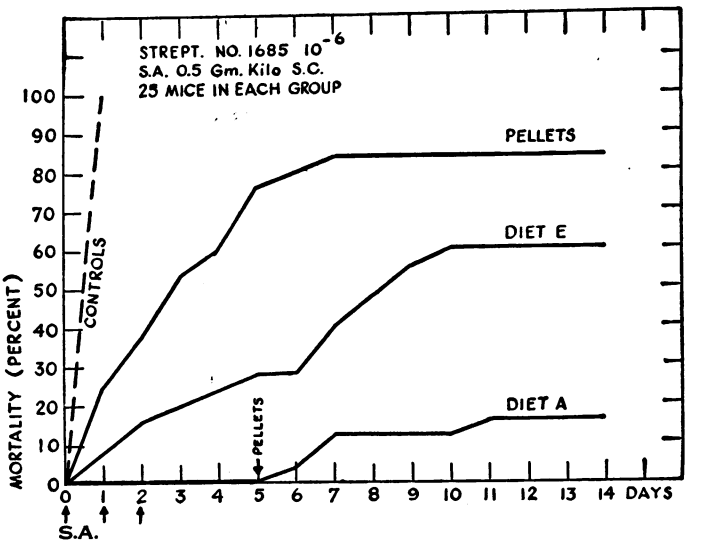

FIGURE 2.—Comparison of therapeutic response to sulfanilamide in mice on a protein-free diet (A), on an 18 percent casein diet (E), and on pellets.

were excluded from the test since death was not due to the bacterial infection.

This experiment was repeated with essentially similar results, employing commercial casein (not purified) and omitting the addition of synthetic vitamins (table 2, fig. 3). A group of animals fed upon a diet of pellets was also included in this experiment. The mortality

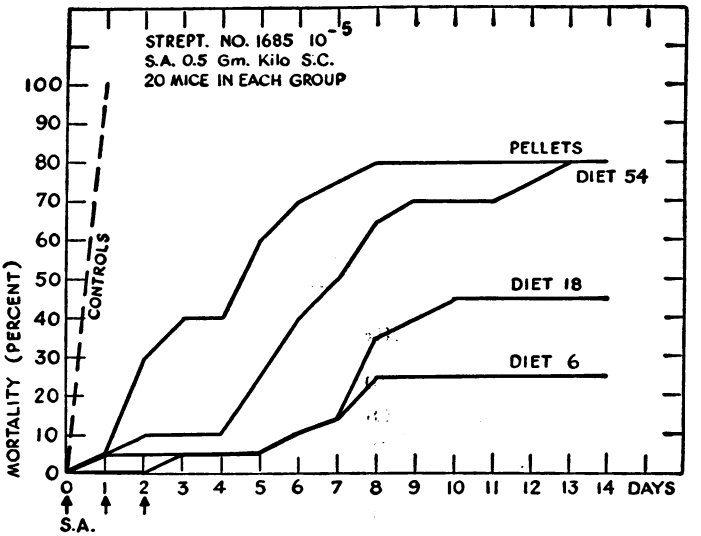

FIGURE 3.—Effect of varying the amount of protein on the therapeutic response to sulfanilamide. Diet numbers refer to casein content.

was similar to that with diet 54, although the pellet diet was slightly more antagonistic than diet 54 as shown by the mean survival time. These results, along with other comparisons made above, indicate that the antagonistic action of the pellet diet, as compared with the casein diet, is out of proportion to the protein content. Either the nature of the protein, or other ingredients in the pellet diet, must play a part in this effect.[4] Only a small percentage of the protein in pellets is present as casein.

[4] Quantitative studies of food intake indicate that this difference may largely be due to greater food consumption on the pellet diet.

TABLE 2.—*Antagonism of therapeutic effect of sulfanilamide by high protein diets. The diet numbers refer to the percentage of casein (see text). In the upper experiment commercial casein was used. In the lower, purified casein plus vitamin supplements were employed. Three daily doses of sulfanilamide in upper, 4 in lower experiment. Diets continued 3 additional days*

Diet No.	Number of mice	Mean weight		Mean daily food intake	Streptococcus No. 1685, dilution of culture	Deaths in days										Mortality, percent
		At onset	At inoculation			1	2	3	4	5	6	7	8	9	10	11-14
		gm.	*gm.*	*gm.*												
6	20	26.19	26.6	4.8	10^{-6}	----	----	----	----	1	2	----	2	----	----	----	25
18	20	26.0	26.5	4.4	-------	1	----	----	----	----	2	----	4	----	2	----	45
54	20	26.42	26.2	2.83	-------	1	1	----	----	5	2	1	3	1	----	2	80
Pellets	20	24.9	25.66	------	-------	1	5	2	1	3	3	1	----	----	----	----	80
0	20	17.2	14.05	3.0	2×10^{-6}	----	----	----	4	----	----	----	----	----	1	----	25
6	25	15.86	15.2	3.2	-------	----	1	----	----	----	1	2	----	1	----	----	20
18	24	16.27	17.3	3.32	-------	----	9	1	----	----	----	----	2	4	----	----	66.6
54	24	16.8	16.5	2.58	-------	1	13	3	2	----	1	----	----	----	----	----	83.3

MECHANISM OF THE DIETARY INFLUENCE

The exact nature of the influence of diet upon the therapeutic activity of sulfanilamide remains to be clarified. The above results indicate that the protein fraction of the diet is involved in the antagonism, and several experiments were undertaken to throw further light upon the basis of this effect.

Resistance of the host to infection.—The virulence of streptococcus No. 1685 was tested upon a group of mice that had been fed a protein-free diet (0) for 5 days and upon a similar group fed pellets. No differences in susceptibility to infection were seen.

Dilution of culture	Number of mice in each group	Mortality	
		Diet 0	Pellets
		Percent	*Percent*
10^{-6}	4	100	100
10^{-7}	8	87	100
10^{-8}	8	100	87
10^{-9}	8	37	25

Delayed action of sulfanilamide.—The possibility that sulfanilamide might induce more prolonged effect in animals upon a low protein diet was next investigated. Groups of mice on pellets and on diet 0 for 5 days were given 0.5 gm. per kilo of sulfanilamide subcutaneously

and then inoculated 24 and 48 hours later with streptococcus No. 1685, 10^{-6} dilution.

Diet	Interval following administration of sulfanilamide	Number of mice	Deaths in days		
			1	2	3
	Hours				
No. 0	24	10	7	3	
Pellets	24	10	10		
No. 0	48	10	4	4	1
Pellets	48	10	8	2	

The effects of the drug largely disappear, although some prolongation of the survival time is seen for at least 48 hours after the administration of sulfanilamide in those animals on the low protein diet as compared with those on pellets.

Sulfanilamide in the blood and urine.—Sulfanilamide was determined in mice following the technique of Marshall and Cutting (*8*). For animals under test, where the sacrifice of the animal was not desired, determinations were carried out upon 0.02 cc. of blood obtained from the tail.

In other experiments carried out with animals not infected with streptococci, groups of 6 were kept in small metabolism cages; the urines were collected at intervals following the injection of sulfanilamide, and macro determinations of the drug in the blood were made upon samples obtained by decapitation.

Confirmatory of the results of Smith et al. (*3*) in rats, consistently higher concentrations of sulfanilamide were observed in the blood of mice upon the protein-free diet (tables 3 and 4). Eighteen determinations of free sulfanilamide in three groups of mice on diet 0 gave an average concentration at 6 hours after the drug of 14.8 mg. percent (standard deviation ± 3.464, standard error ± 0.816), as compared with 6.23 mg. percent (standard deviation ± 2.738, standard error ± 0.645) on the pellet diet. In the sacrifice experiments sufficient blood was obtained to estimate total sulfanilamide and to obtain accurate values for the 24-hour interval. On diet 0 at 24 hours after the drug (12 mice) the free sulfanilamide in the blood averaged 0.52 mg. percent and the total (free plus acetylated) averaged 1.34 mg. percent as compared with 0.17 and 0.63 mg. percent, respectively, in the mice on pellets. The degree of acetylation in the animals on pellets was slightly greater than on diet 0, but insufficient to account for the large differences in concentration. This was substantiated by the results with urinary excretion.

TABLE 3.—*Sulfanilamide in the blood of mice with different diets under therapeutic test. Determinations upon 0.02 cc. of blood from tail. Mean values given in parentheses*

Interval, in hours, after sulfanilamide administration	Number of mice	Blood sulfanilamide (free), mg. percent	
		Diet A	Diet E
2	6	29.4–46.4 (34.4)	25.4–39.4 (29.6)
6	6	7.4–12.9 (10.8)	5.0–11.4 (8.4)
24	6	1.4–5.4 (2.8)	0.4–1.4 (0.8)
		Diet 0	Pellets
6	6	9.4–16.8 (15)	3.4–9.4 (7.4)
24	6	(1)	(1)
6	6	7.8–15.4 (13.1)	2.8–6.4 (5.1)
24	6	(1)	(1)

[1] Traces.

In three groups of 6 mice each on diet 0, the urinary excretion at 6 hours averaged 36.8 percent free and 45.3 percent total sulfanilamide, as compared with 39.6 and 49.4 percent, respectively, for animals on pellets. The 24-hour excretion in two groups of mice on diet 0 averaged 55.3 percent free and 70.2 percent total sulfanilamide as compared with 47.3 percent free and 67.7 percent total, on a diet of pellets (table 4).

TABLE 4.—*Sulfanilamide in the blood and urine of normal mice on a protein-free diet (0) for 5 days and mice on pellets. Blood obtained by decapitation. Individual determinations upon the blood in upper group, with mean values in parentheses. Pooled blood used in the lower experiment*

Diet	Interval, in hours, after sulfanilamide administration	Number of mice	Sulfanilamide in urine		Sulfanilamide in blood, mg. percent	
			Free	Total	Free	Total
			Percent	*Percent*		
0	6	6	28	40	9–23 (15.6)	12–25 (19)
Pellets	6	6	40	45	2.5–12.5 (5.6)	3.9–18 (7.7)
0	6	6	38	44.3		
0	6	6	44.3	51.6		
Pellets	6	6	41.6	55.5		
Pellets	6	6	36	48.3		
0	24	6	51.3	65.9	0.6	1.5
0	24	6	59.3	74.6	.45	1.18
Pellets	24	6	50.6	72.1	.2	.66
Pellets	24	6	44	63.3	.15	.6

From the evidence at hand the higher concentrations of sulfanilamide in the blood in mice on low protein diets cannot be accounted for by either decreased acetylation or delayed excretion.[5]

Explanation of the above results must await further investigation of dietary influence upon the absorption, excretion, and fate in the body of sulfanilamide. While the concentration of the drug in the blood must be an important factor in these results, it is believed that substances inhibitory to the action of sulfanilamide may also be involved. The work of Smith (*3*) has shown that sulfanilamide is more toxic in rats upon a low protein diet. The factor of drug toxicity cannot therefore be involved in the decreased mortality observed upon low protein diets. It must be remembered, however, that low protein diets may be associated with potential increases in toxicity of the drug. Further investigation must establish whether the same constituent of the proteins is responsible for both effects.

Apart from any therapeutic significance these experiments emphasize the desirability of standardization of the diet in the evaluation of chemotherapeutic agents. This influence may be an important factor in the discordant results often obtained in different laboratories, as well as the variations encountered in the same laboratory.

SUMMARY

Wide variations in the therapeutic response to sulfanilamide can be produced in mice by alterations in the diet.

A study of dietary constituents indicates that the protein fraction is important in the inhibition of the action of sulfanilamide.

Mice on a diet deficient in proteins have shown higher concentrations of sulfanilamide in the blood.

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(*5*) Woods, D. D.: The relation of p-aminobenzoic acid to the mechanism of action of sulfanilamide. Brit. J. Exp. Path., **21**:74 (1940).

(*6*) Selbie, F. R.: The inhibition of action of sulfanilamide in mice by p-aminobenzoic acid. Brit. J. Exp. Path., **21**:90 (1940).

[5] By adapting a micro technique for the determination of phenolsulfonephthalein in the serum it was shown that a delay in removal of this dye from the blood (see Rosenthal, S. M.: Proc. Soc. Exp. Biol. and Med., **21**:72 (1923)) was apparent in normal mice after 4 days upon diet No. 6, becoming pronounced on the sixth day. This indicates that altered renal function is an important factor in the retention of sulfanilamide on low protein diets.

(7) McCollum, E. V., and Davis, M.: The essential factors in the diet during growth. J. Biol. Chem., 23:235 (1915).
(8) Marshall, E. K., Jr., and Cutting, W. C.: Absorption and excretion of sulfanilamide in the mouse and rat. Bull. Johns Hopkins Hosp., 63:328 (1938).

DEATHS DURING WEEK ENDED SEPTEMBER 6, 1941

[From the Weekly Mortality Index, issued by the Bureau of the Census, Department of Commerce]

	Week ended Sept. 6, 1941	Corresponding week, 1940
Data from 87 large cities of the United States:		
Total deaths	7,404	7,288
Average for 3 prior years	7,031	
Total deaths, first 36 weeks of year	305,575	306,219
Deaths per 1,000 population, first 36 weeks of year, annual rate	11.9	11.9
Deaths under 1 year of age	521	441
Average for 3 prior years	468	
Deaths under 1 year of age, first 36 weeks of year	18,827	17,979
Data from industrial insurance companies:		
Policies in force	64,453,029	64,915,823
Number of death claims	7,821	8,420
Death claims per 1,000 policies in force, annual rate	6.3	6.8
Death claims per 1,000 policies, first 36 weeks of year, annual rate	9.6	9.8

PREVALENCE OF DISEASE

No health department, State or local, can effectively prevent or control diseases without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

REPORTS FROM STATES FOR WEEK ENDED SEPTEMBER 13, 1941

Summary

A slight increase in the incidence of poliomyelitis was recorded for the current week, with 595 cases reported as compared with 584 for the preceding week. The largest increases were recorded for the New England States (27 to 48) and the Middle Atlantic (169 to 213), and the largest decreases were reported for the East South Central (132 to 86), South Atlantic (115 to 80), and West North Central States (36 to 28).

The following listed 13 States reported 15 or more cases during the current week (last week's figures in parentheses): New York, 109 (71)—53 in New York City and 56 in the State outside New York City; Pennsylvania, 63 (66); New Jersey, 41 (32); Alabama, 38 (66); Ohio, 35 (33); Tennessee, 29 (38); Georgia, 26 (49); Illinois, 25 (21); Minnesota, 24 (23); Michigan, 20 (7); Connecticut, 19 (6); Maryland, 17 (16); Massachusetts, 16 (18). Last week also 13 States reported 15 or more cases, but for the current week Virginia and Kentucky dropped out of the group while Connecticut and Michigan were added.

To date this year (first 37 weeks) a total of 5,204 cases of poliomyelitis has been reported in the United States, as compared with 6,391 in 1937 and 4,856 in 1940 for the corresponding period.

Of a total of 882 cases of influenza reported for the current week, 530 cases occurred in Texas. While the incidence of the disease during the past summer has not been alarmingly high, it has been continuously above the 5-year (1936–40) median, due entirely to the large number of cases reported in Texas, which has accounted for about 41 percent of the total for the country as a whole.

Encephalitis continued to decline in all of the West North Central States where the disease has been epidemic during the past summer.

No cases of Rocky Mountain spotted fever were reported in the Mountain States during the current week, while 6 cases were reported in States east of that area.

Of 136 cases of endemic typhus fever, 56 occurred in Georgia, 23 in Texas, 16 in Louisiana, 13 in Florida, and 10 in Alabama. A total of 1,615 cases has been reported this year to date, as compared with 1,247 from January to September, inclusive, in 1940 and 2,140 for the same period in 1939.

The death rate for the current week in 88 large cities in the United States was 10.4 per 1,000 population, the same as for the preceding week. The 3-year (1938–40) average for the corresponding period is 10.3.

Telegraphic morbidity reports from State health officers for the week ended September 13, 1941, and comparison with corresponding week of 1940 and 5-year median

In these tables a zero indicates a definite report, while leaders imply that, although none were reported, cases may have occurred.

Division and State	Diphtheria			Influenza			Measles			Meningitis, meningococcus		
	Week ended—		Median 1936–40	Week ended—		Median 1936–40	Week ended—		Median 1936–40	Week ended—		Median 1936–40
	Sept. 13, 1941	Sept. 14, 1940		Sept. 13, 1941	Sept. 14, 1940		Sept. 13, 1941	Sept. 14, 1940		Sept. 13, 1941	Sept. 14, 1940	
NEW ENG.												
Maine	0	1	1	1	-------	-------	25	12	1	0	1	0
New Hampshire	0	0	0	-------	-------	-------	2	0	2	0	0	0
Vermont	0	1	1	-------	-------	-------	4	0	0	0	1	0
Massachusetts	4	0	2	-------	-------	-------	33	65	22	3	1	1
Rhode Island	0	0	0	-------	-------	-------	9	0	2	0	0	0
Connecticut	0	0	2	1	3	1	6	4	4	1	0	0
MID. ATL.												
New York [1]	8	7	10	[2] 0	[2] 5	[2] 5	81	77	60	5	8	7
New Jersey	1	3	3	4	-------	4	19	33	20	1	0	0
Pennsylvania	12	7	17	1	-------	-------	61	35	33	2	1	3
E. NO. CEN.												
Ohio	10	4	14	4	12	12	23	13	13	0	0	1
Indiana [3]	1	2	10	4	3	8	2	5	3	0	0	0
Illinois [1 3]	17	14	18	-------	1	5	35	15	15	1	3	1
Michigan [4]	4	0	7	-------	2	1	73	44	14	0	0	1
Wisconsin	0	0	2	7	21	20	77	61	40	1	3	1
W. NO. CEN.												
Minnesota	4	1	2	1	1	1	0	1	6	0	0	0
Iowa [3]	1	2	2	4	3	-------	16	18	4	0	0	0
Missouri	3	1	13	-------	2	2	4	2	3	0	1	1
North Dakota	1	1	1	-------	-------	2	0	0	2	0	0	0
South Dakota	3	1	1	-------	-------	-------	0	1	1	0	0	0
Nebraska	0	0	1	-------	-------	-------	2	1	2	0	0	0
Kansas	3	7	7	2	1	1	3	14	8	1	0	0
SO. ATL.												
Delaware	0	0	0	-------	-------	-------	0	2	-------	1	0	0
Maryland [1 3 4]	1	2	4	2	2	2	11	2	5	0	0	1
Dist. of Col	1	2	2	-------	-------	-------	3	0	0	0	0	0
Virginia	6	8	33	60	47	-------	15	10	7	1	0	1
West Virginia [4]	5	6	10	5	11	13	29	3	3	0	3	3
North Carolina [1]	40	26	72	-------	2	1	40	3	4	0	1	1
South Carolina [1]	36	9	18	123	148	119	32	4	7	2	0	0
Georgia [1]	24	16	30	7	2	-------	16	1	-------	0	0	0
Florida [1]	1	3	8	7	2	-------	4	1	3	0	0	0
E. SO. CEN.												
Kentucky	7	13	13	-------	5	5	29	3	12	1	0	0
Tennessee [1 3]	10	5	22	10	3	9	13	10	4	1	1	1
Alabama [1]	19	20	31	3	6	8	5	2	2	1	0	2
Mississippi [1 4]	9	12	15	-------	-------	-------	-------	0	-------	0	0	1
W. SO. CEN.												
Arkansas	11	12	17	2	1	3	28	1	1	0	0	0
Louisiana [1]	5	8	8	3	2	2	7	0	0	1	0	1
Oklahoma	13	8	8	8	44	16	6	1	1	1	0	1
Texas [1 4]	38	14	33	530	79	79	48	22	20	1	0	1
MOUNTAIN												
Montana	0	1	1	-------	2	-------	3	3	5	0	1	1
Idaho	0	0	1	-------	-------	-------	2	0	3	0	0	0
Wyoming	0	1	1	4	-------	-------	3	0	0	0	0	0
Colorado	14	3	3	19	1	-------	5	3	3	0	0	0
New Mexico	0	4	2	1	2	-------	2	1	1	0	0	0
Arizona	0	0	2	36	13	18	52	16	2	1	0	0
Utah [4]	0	2	0	-------	-------	-------	1	6	6	0	0	0
Nevada	0	-------	-------	-------	-------	-------	0	-------	-------	0	-------	-------
PACIFIC												
Washington	0	3	0	-------	-------	-------	7	8	10	1	1	0
Oregon	3	2	1	6	6	9	8	16	7	0	0	0
California	11	17	17	21	12	12	74	42	38	1	1	0
Total	326	249	504	882	444	385	918	561	561	28	27	35
37 weeks	8,750	9,707	15,435	602,525	170,891	153,176	833,999	231,174	271,581	1,541	1,262	2,285

See footnotes at end of table.

Telegraphic morbidity reports from State health officers for the week ended September 13, 1941, and comparison with corresponding week of 1940 and 5-year median—Con.

Division and State	Poliomyelitis			Scarlet fever			Smallpox			Typhoid and paratyphoid fever		
	Week ended—		Median 1936–40	Week ended—		Median 1936–40	Week ended—		Median 1936–40	Week ended—		Median 1936–40
	Sept. 13, 1941	Sept. 14, 1940		Sept. 13, 1941	Sept. 14, 1940		Sept. 13, 1941	Sept. 14, 1940		Sept. 13, 1941	Sept. 14, 1940	
NEW ENG.												
Maine	3	1	1	6	8	5	0	0	0	4	3	1
New Hampshire	7	0	0	3	2	1	0	0	0	1	0	0
Vermont	1	2	1	1	3	3	0	0	0	1	1	0
Massachusetts	16	4	4	59	37	34	0	0	0	5	1	5
Rhode Island	2	1	1	4	1	1	0	0	0	0	0	0
Connecticut	19	3	1	10	11	11	0	0	0	1	3	4
MID. ATL.												
New York [1]	109	14	14	72	72	72	0	0	0	30	16	21
New Jersey	41	3	3	15	24	16	0	0	0	7	5	11
Pennsylvania	63	14	14	40	44	73	0	0	0	24	22	37
E. NO. CEN.												
Ohio	35	53	18	49	52	80	0	1	0	14	8	23
Indiana [2]	7	58	6	12	14	30	1	0	2	2	8	9
Illinois [1 2]	25	59	52	44	100	94	0	0	0	6	12	20
Michigan [4]	20	160	57	47	55	59	2	0	0	7	3	10
Wisconsin	6	31	4	52	37	39	3	0	0	9	0	1
W. NO. CEN.												
Minnesota	24	9	9	11	16	23	0	0	0	2	4	2
Iowa [3]	0	100	12	10	25	24	0	1	1	5	1	2
Missouri	1	36	5	8	15	25	1	0	0	6	10	25
North Dakota	1	2	0	1	0	4	0	8	0	0	1	1
South Dakota	0	7	2	7	3	13	0	3	1	3	0	1
Nebraska	1	14	5	8	1	10	0	0	1	0	0	0
Kansas	1	49	5	44	32	31	0	0	0	3	10	10
SO. ATL.												
Delaware	0	0	0	8	4	3	0	0	0	0	0	1
Maryland [1 3 4]	17	1	1	16	6	13	0	0	0	9	4	11
Dist. of Col	3	0	1	11	3	5	0	0	0	0	1	1
Virginia	11	16	3	5	13	13	0	0	0	14	21	18
West Virginia [4]	2	48	2	16	16	30	0	0	0	8	8	16
North Carolina [1]	9	10	3	40	46	46	0	0	0	17	13	13
South Carolina [1]	8	2	1	8	9	9	0	0	0	5	15	15
Georgia [1]	26	4	4	8	12	12	0	0	0	18	13	13
Florida [1]	4	2	1	2	1	2	0	0	0	4	4	4
E. SO. CEN.												
Kentucky	14	16	4	25	25	31	0	0	0	13	23	30
Tennessee [1 3]	29	4	1	32	26	25	2	0	0	5	20	16
Alabama [1]	38	1	3	18	15	15	0	0	0	7	12	12
Mississippi [1 4]	5	3	4	11	11	8	0	0	0	8	9	9
W. SO. CEN.												
Arkansas	5	1	1	1	11	6	1	0	0	15	26	17
Louisiana [1]	1	3	1	2	1	4	0	0	0	20	13	15
Oklahoma	2	8	2	10	16	12	0	1	1	11	12	23
Texas [1 4]	4	8	8	20	12	24	0	0	0	35	47	49
MOUNTAIN												
Montana	2	4	1	9	11	11	0	0	2	2	2	3
Idaho	1	3	1	3	0	2	0	0	0	0	12	4
Wyoming	0	2	1	1	1	3	0	0	0	0	2	1
Colorado	6	4	4	14	13	9	0	0	2	4	7	6
New Mexico	1	2	2	1	2	6	0	0	0	3	3	10
Arizona	0	0	0	1	2	2	0	0	0	1	0	3
Utah [4]	3	5	4	1	8	13	0	0	0	0	1	0
Nevada	0	------	------	0	------	------	0	------	------	0	------	------
PACIFIC												
Washington	8	12	2	9	10	13	0	0	2	2	1	5
Oregon	6	4	2	2	3	10	0	0	0	3	2	5
California	8	14	14	42	55	72	0	0	1	3	10	10
Total	595	797	501	819	884	1,022	10	14	42	337	389	559
37 weeks	5,204	4,856	3,946	94,578	121,688	140,899	1,207	2,002	8,184	5,836	6,636	9,268

See footnotes at end of table.

Telegraphic morbidity reports from State health officers for the week ended September 13, 1941, and comparison with corresponding week of 1940—Continued

Division and State	Whooping cough	
	Week ended—	
	Sept. 13, 1941	Sept. 14, 1940
NEW ENG.		
Maine	6	27
New Hampshire	4	0
Vermont	0	1
Massachusetts	194	130
Rhode Island	47	1
Connecticut	41	25
MID. ATL.		
New York [1]	319	255
New Jersey	192	135
Pennsylvania	216	336
E. NO. CEN.		
Ohio	317	220
Indiana [3]	12	31
Illinois [1 3]	237	112
Michigan [4]	340	285
Wisconsin	239	127
W. NO. CEN.		
Minnesota	31	57
Iowa [3]	27	17
Missouri	20	41
North Dakota	5	4
South Dakota	19	9
Nebraska	2	2
Kansas	97	33
SO. ATL.		
Delaware	2	12
Maryland [1 3 4]	39	65
Dist. of Col	24	4
Virginia	44	56
West Virginia [4]	11	38
North Carolina [1]	83	86
SO. ATL.—continued		
South Carolina [1]	69	26
Georgia [1]	5	7
Florida [1]	8	1
E. SO. CEN.		
Kentucky	71	79
Tennessee [1 3]	53	29
Alabama [1]	25	11
Mississippi [1 4]	-------	-------
W. SO. CEN.		
Arkansas	18	5
Louisiana [1]	2	6
Oklahoma	20	8
Texas [1 4]	127	96
MOUNTAIN		
Montana	44	8
Idaho	17	0
Wyoming	20	1
Colorado	75	15
New Mexico	25	6
Arizona	14	3
Utah [4]	33	22
Nevada	24	-------
PACIFIC		
Washington	76	53
Oregon	29	11
California	223	228
Total	3,555	2,724
37 weeks	159,503	117,570

[1] Typhus fever, week ended Sept. 13, 1941, 136 cases, as follows: New York, 1; Illinois, 1; Maryland, 1; North Carolina, 3; South Carolina, 4; Georgia, 56; Florida, 13; Tennessee, 2; Alabama, 10; Mississippi, 6; Louisiana, 16; Texas, 23.

[2] New York City only.

[3] Rocky Mountain spotted fever, week ended Sept. 13, 1941, 6 cases, as follows: Indiana, 1; Illinois, 1; Iowa, 2; Maryland, 1; Tennessee, 1.

[4] Period ended earlier than Saturday.

WEEKLY REPORTS FROM CITIES

City reports for week ended August 30, 1941

This table lists the reports from 128 cities of more than 10,000 population distributed throughout the United States, and represents a cross section of the current urban incidence of the diseases included in the table.

State and city	Diphtheria cases	Influenza		Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases	Deaths, all causes
		Cases	Deaths								
Maine:											
Portland	0	------	0	0	1	0	0	1	0	6	21
New Hampshire:											
Concord	0	------	0	0	0	0	0	1	0	0	7
Manchester	0	------	0	0	0	2	0	0	0	0	19
Nashua	0	------	0	0	0	0	0	0	0	0	3
Vermont:											
Burlington	0	------	0	0	0	0	0	0	0	0	7
Rutland	0	------	0	0	0	0	0	0	0	0	9
Massachusetts:											
Boston	0	------	0	10	3	18	0	8	0	31	157
Fall River	0	------	0	0	0	1	0	0	0	2	27
Springfield	0	------	0	1	0	2	0	0	0	5	27
Worcester	0	------	0	4	5	2	0	1	0	6	49
Rhode Island:											
Pawtucket	0	------	0	0	0	0	0	0	0	0	15
Providence	1	------	0	3	0	3	0	1	0	12	48
Connecticut:											
Bridgeport	0	------	0	0	1	1	0	1	0	2	29
Hartford	0	------	0	3	0	1	0	0	0	0	25
New Haven	0	------	0	5	1	0	0	0	0	3	42
New York:											
Buffalo	0	------	0	0	8	3	0	2	0	19	115
New York	9	------	0	20	25	32	0	64	7	154	1,203
Rochester	0	------	0	0	0	0	0	0	0	3	63
Syracuse	0	------	0	3	1	0	0	1	0	28	44
New Jersey:											
Camden	0	------	0	0	0	2	0	0	0	0	24
Newark	0	1	0	1	5	3	0	2	0	37	81
Trenton	0	------	0	1	0	1	0	2	0	0	34
Pennsylvania:											
Philadelphia	3	------	2	6	8	19	0	10	3	41	364
Pittsburgh	0	------	0	0	4	2	0	7	1	28	144
Reading	0	------	0	0	0	1	0	0	0	1	25
Scranton	0	------	--------	0	-------	0	0	-------	0	0	--------
Ohio:											
Cincinnati	1	------	0	0	1	5	0	1	0	5	92
Cleveland	0	4	0	1	1	6	0	8	1	56	156
Columbus	0	------	0	2	0	1	0	1	0	20	78
Toledo	0	------	0	3	1	3	0	0	2	39	59
Indiana:											
Anderson	0	------	0	0	0	0	0	0	0	0	6
Fort Wayne	0	------	0	0	1	0	0	1	0	0	16
Indianapolis	1	------	0	0	2	2	0	5	0	3	105
Muncie	0	------	0	1	2	0	0	0	0	0	8
Terre Haute	0	------	0	0	1	0	0	2	0	0	16
Illinois:											
Alton	0	------	0	0	0	0	0	0	2	0	8
Chicago	5	1	0	4	10	14	0	33	2	140	535
Elgin	0	------	0	0	1	0	0	0	0	4	14
Springfield	0	------	0	1	1	0	0	1	0	0	22
Michigan:											
Detroit	2	------	0	21	9	10	0	12	1	47	197
Flint	0	------	0	0	1	0	0	0	0	3	17
Grand Rapids	0	------	0	0	1	1	0	0	0	9	38
Wisconsin:											
Kenosha	0	------	0	0	0	0	0	0	0	9	5
Madison	0	------	0	9	0	0	0	0	0	5	19
Milwaukee	0	1	1	8	1	6	0	1	0	151	90
Racine	0	------	0	2	0	1	0	0	0	5	14
Superior	0	------	0	0	0	0	0	0	0	0	5
Minnesota:											
Duluth	0	------	0	0	1	2	0	0	0	8	23
Minneapolis	0	------	0	0	1	4	0	0	0	5	82
St. Paul	0	------	0	1	3	0	0	1	0	15	55
Iowa:											
Des Moines	0	------	--------	1	-------	0	0	-------	0	2	26
Sioux City	0	------	--------	0	-------	0	0	-------	0	2	--------
Waterloo	0	------	--------	1	-------	0	0	-------	0	5	--------

City reports for week ended August 30, 1941—Continued

State and city	Diphtheria cases	Influenza		Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases	Deaths, all causes
		Cases	Deaths								
Missouri:											
Kansas City	0	------	0	1	1	4	0	3	1	1	87
St. Joseph	0	------	0	0	2	0	0	1	0	0	10
St. Louis	1	------	0	2	4	4	0	10	0	23	169
North Dakota:											
Fargo	0	------	0	0	0	0	0	1	0	0	12
Grand Forks	0	------	-------	0	-------	0	0	-------	0	0	-------
Minot	0	------	-------	1	-------	0	0	-------	0	1	6
South Dakota:											
Aberdeen	0	------	-------	0	-------	2	0	-------	0	1	-------
Nebraska:											
Lincoln	0	------	-------	0	-------	0	0	-------	0	3	-------
Omaha	0	------	0	1	0	0	0	0	1	0	31
Kansas:											
Lawrence	0	------	0	0	0	0	0	0	0	0	1
Topeka	0	------	0	0	1	5	0	1	0	10	13
Wichita	0	------	0	0	2	3	0	0	1	4	28
Delaware:											
Wilmington	0	------	0	0	0	2	0	0	0	1	27
Maryland:											
Baltimore	0	2	0	10	6	7	0	8	4	50	187
Cumberland	0	------	0	0	0	0	0	0	0	0	13
Frederick	0	------	0	0	0	0	0	0	0	0	-------
Dist. of Col.:											
Washington	1	------	0	6	7	6	0	10	1	15	138
Virginia:											
Lynchburg	0	------	0	0	0	1	0	0	0	0	9
Norfolk	1	------	0	0	2	0	0	0	0	1	33
Richmond	1	------	0	1	3	0	0	2	0	0	43
Roanoke	0	------	0	0	0	0	0	1	0	0	13
West Virginia:											
Charleston	0	------	0	0	2	0	0	1	0	1	20
Huntington	0	------	-------	2	-------	0	0	-------	1	1	-------
Wheeling	0	------	0	2	1	0	0	0	0	4	23
North Carolina:											
Gastonia	0	------	-------	0	-------	1	0	-------	0	1	-------
Raleigh	0	------	0	1	0	1	0	2	0	12	13
Wilmington	0	------	0	0	3	0	0	1	0	9	11
Winston-Salem	0	------	0	1	0	0	0	0	0	2	25
South Carolina:											
Charleston	0	------	0	0	1	0	0	0	2	1	14
Florence	0	------	-------	0	-------	0	0	-------	0	0	-------
Greenville	1	------	0	0	0	0	0	0	0	1	14
Georgia:											
Atlanta	0	------	0	2	3	4	0	4	0	4	60
Brunswick	0	------	0	0	0	0	0	0	0	0	2
Savannah	0	------	0	2	0	0	0	1	0	0	23
Florida:											
Miami	0	1	1	1	0	0	0	1	1	3	47
St. Petersburg	0	------	1	0	3	0	0	0	0	0	19
Tampa	0	1	0	0	1	0	0	2	0	0	17
Kentucky:											
Ashland	0	------	0	0	0	0	0	0	1	1	9
Covington	0	------	0	0	0	1	0	1	0	0	10
Lexington	0	------	0	0	0	0	0	3	1	6	13
Tennessee:											
Knoxville	2	------	1	0	0	0	0	1	0	0	23
Memphis	0	------	2	1	7	1	0	4	0	9	67
Nashville	0	------	0	0	1	2	0	3	0	17	55
Alabama:											
Birmingham	1	------	0	0	2	0	0	3	2	1	55
Mobile	1	------	1	1	0	0	0	0	0	0	26
Montgomery	0	------	-------	0	-------	1	0	-------	0	2	-------
Arkansas:											
Fort Smith	0	------	-------	0	-------	0	0	-------	0	0	-------
Little Rock	0	------	0	0	0	0	0	2	0	0	23
Louisiana:											
Lake Charles	0	------	0	0	0	0	0	0	0	0	2
New Orleans	0	------	0	0	12	0	0	15	0	0	164
Shreveport	0	------	0	0	7	1	0	2	0	0	65
Oklahoma:											
Oklahoma City	0	------	0	0	1	0	0	0	0	1	36
Tulsa	0	------	0	0	0	2	0	0	0	0	9
Texas:											
Dallas	1	------	0	8	0	1	0	2	0	10	53
Galveston	0	------	0	0	0	0	0	1	0	0	17
Houston	2	------	0	1	4	0	0	4	1	0	78
San Antonio	0	------	0	1	6	2	0	9	0	0	51

City reports for week ended August 30, 1941—Continued

State and city	Diphtheria cases	Influenza		Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases	Deaths, all causes
		Cases	Deaths								
Montana:											
Billings	0	------	0	0	1	0	0	0	0	3	4
Great Falls	0	------	0	0	0	0	0	0	0	2	12
Helena	0	------	0	0	0	0	0	0	0	2	9
Missoula	0	------	0	0	1	0	0	0	0	0	5
Colorado:											
Colorado Springs	0	------	0	1	0	0	0	1	0	7	14
Denver	0	12	0	5	2	2	0	3	0	51	85
Pueblo	0	------	0	0	0	3	0	0	0	0	11
New Mexico:											
Albuquerque	0	------	0	0	1	0	0	1	0	0	7
Arizona:											
Phoenix	0	3	--------	0	-------	0	0	-------	0	1	--------
Utah:											
Salt Lake City	0	------	0	1	1	2	0	0	0	16	29
Washington:											
Seattle	0	------	1	0	1	1	0	3	2	25	70
Spokane	0	------	0	1	0	2	0	0	0	7	28
Tacoma	0	------	0	0	0	0	0	1	0	3	28
Oregon:											
Portland	0	------	0	0	1	1	0	0	0	4	66
Salem	0	------	--------	0	-------	0	0	-------	0	2	--------
California:											
Los Angeles	3	5	0	40	4	7	0	18	1	35	340
Sacramento	0	------	0	2	2	0	0	3	0	0	35
San Francisco	0	------	0	2	2	2	0	5	0	11	160

State and city	Meningitis, meningococcus		Poliomyelitis cases	State and city	Meningitis, meningococcus		Poliomyelitis cases
	Cases	Deaths			Cases	Deaths	
Massachusetts:				District of Columbia:			
Boston	0	0	10	Washington	0	0	8
Worcester	0	0	1	Virginia:			
Rhode Island:				Norfolk	0	0	1
Providence	0	0	3	Richmond	1	0	0
Connecticut:				Roanoke	1	0	0
Bridgeport	0	0	2	West Virginia:			
New Haven	0	0	1	Huntington	0	0	1
New York:				Wheeling	0	1	0
New York	1	0	47	Georgia:			
Rochester	0	0	5	Atlanta	1	1	3
Pennsylvania:				Florida:			
Philadelphia	0	0	6	Tampa	0	0	1
Pittsburgh	0	0	1	Tennessee:			
Scranton	0	0	1	Nashville	0	0	4
Ohio:				Alabama:			
Cincinnati	0	0	1	Birmingham	0	0	4
Cleveland	0	0	20	Montgomery	0	0	3
Indiana:				Arkansas:			
South Bend	0	0	1	Little Rock	0	0	1
Terre Haute	0	0	1	Texas:			
Illinois:				Houston	1	0	0
Chicago	1	0	13	Montana:			
Michigan:				Billings	0	0	1
Detroit	0	0	13	Colorado:			
Wisconsin:				Pueblo	1	0	0
Superior	0	0	2	Utah:			
Minnesota:				Salt Lake City	0	0	5
Duluth	0	0	1	Oregon:			
Minneapolis	0	0	4	Portland	0	0	2
St. Paul	0	0	12	California:			
South Dakota:				Los Angeles	0	0	2
Aberdeen	0	0	1	Sacramento	0	0	1
Maryland:							
Baltimore	1	0	14				

Encephalitis, epidemic or lethargic.—Cases: New York, 3; Rochester, 1; Philadelphia, 1; Duluth, 1; Minneapolis, 6; St. Paul, 2; Sioux City, 5; Fargo, 4; Grand Forks (delayed report), 4; Minot, 1; Aberdeen, 1; Omaha, 5; Billings, 1; Great Falls, 1; Denver, 8. Deaths: New York, 1; Philadelphia, 1; Indianapolis, 1; St. Paul, 1; Sioux City, 1; Aberdeen, 1; Omaha, 2; Topeka, 1; Denver, 1.

Pellagra.—Cases: Boston, 1; St. Louis, 1.

Typhus fever.—Cases: Charleston, S. C., 1; Atlanta, 1; Savannah, 8; Birmingham, 1; New Orleans, 3; Ft. Worth, 1. Deaths: Houston, 1.

Rates (annual basis) per 100,000 population for a group of 87 selected cities (population, 1940, 33,790,805)

Period	Diphtheria cases	Influenza		Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases
		Cases	Deaths							
Week ended Sept. 6, 1941	5.1	4.2	1.1	29.2	28.7	31.8	0.0	45.2	4.8	182.5
Average, 1936–40	10.8	4.5	1.6	25.9	39.1	35.4	0.3	50.7	11.1	180.5

PLAGUE INFECTION IN GROUND SQUIRREL AND FLEAS IN SISKIYOU COUNTY, CALIF.

Under date of September 4, 1941, Dr. Bertram P. Brown, Director of Public Health of California, reported plague infection proved, by animal inoculation and cultures, in Siskiyou County, Calif., in organs from 1 ground squirrel, *C. douglasii*, submitted to the laboratory on August 21 from a ranch about 1½ miles northwest of Mount Shasta City, in a pool of 17 fleas from 1 ground squirrel, *C. douglasii*, shot on August 9 on a ranch approximately 3½ miles northeast of Weed, and in another pool of 105 fleas from 5 ground squirrels of the same species taken on August 8 from a ranch about 3¼ miles northwest of Weed.

FOREIGN REPORTS

CANADA

Provinces—Communicable diseases—Week ended August 9, 1941.—During the week ended August 9, 1941, cases of certain communicable diseases were reported by the Department of Pensions and National Health of Canada as follows:

Disease	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Total
Cerebrospinal meningitis		1	1	5	12	1	1		1	22
Chickenpox		3		13	63	8	8	19	8	122
Diphtheria	1	9		21	4	2	1			38
Dysentery				13						13
Influenza					1					1
Lethargic encephalitis						19				19
Measles	2	31		55	107	4	17	16	17	249
Mumps				36	52	12	10	3	7	120
Pneumonia		1			2				1	4
Poliomyelitis			33		2	153		15	3	206
Scarlet fever		2	3	21	54	3	4	11	8	106
Tuberculosis	3	5	6	50	50	6	12	1		133
Typhoid and paratyphoid fever	1		2	22	15	1		1	3	45
Whooping cough		1	3	125	106		9	1	27	272

Manitoba—Poliomyelitis.—A total of 51 cases of poliomyelitis was reported in the Province of Manitoba, Canada, for the week ended September 12, as compared with 78 cases for the preceding week. This makes a total of 809 cases to date, which is stated to be 60 per-cent in excess of the number of cases recorded in any previous epidemic in the Province.

The present incidence is reported to have spread from the southern half of the Province, with the exception of a few limited areas in the extreme southwest part, where a high incidence was reported in the epidemic of 1936. The local health authorities are of the opinion that the early appearance of the disease and the accompanying high temperature were factors in the high incidence this year.

Reports state that all suspected cases have been carefully studied and the diagnosis confirmed before they were declared to be positive infections. Paralysis or a degree of muscular weakness subsequently developed in several cases in which the spinal fluid was found to be negative on repeated examinations.

Encephalitis.—During the same week, 22 cases of encephalitis were reported in Manitoba, as compared with 70 for the preceding week,

bringing the total number to date to 431 with 41 deaths. The cases were distributed more or less uniformly over the southern part of the Province, with the incidence increasing toward the southern border. A few cases are now being reported from remote northern areas.

Since the latter part of August, when the temperature dropped precipitately and heavy rains have fallen, there has been a steady decline in cases of both encephalitis and poliomyelitis in Manitoba.

CUBA

Provinces—Notifiable diseases—4 weeks ended August 16, 1941.—During the 4 weeks ended August 16, 1941, cases of certain notifiable diseases were reported in the Provinces of Cuba as follows:

Disease	Pinar del Rio	Habana [1]	Matanzas	Santa Clara	Camaguey	Oriente	Total
Cancer			4	1	1	13	19
Diphtheria		12	4	1	1	4	22
Leprosy		1		1		1	3
Malaria	35	14		19	4	167	229
Measles	1	33					34
Poliomyelitis	1	2				1	4
Rabies		1					1
Scarlet fever		5				1	6
Tetanus, infantile			1				1
Tuberculosis	19	38	26	23	16	47	169
Typhoid fever	26	50	19	47	26	49	226
Undulant fever					1		1
Whooping cough				1		6	7

[1] Includes the city of Habana.

FINLAND

Communicable diseases—June 1941.—During the month of June 1941, cases of certain communicable diseases were reported in Finland as follows:

Disease	Cases	Disease	Cases
Diphtheria	90	Poliomyelitis	6
Influenza	529	Scarlet fever	244
Paratyphoid fever	55	Typhoid fever	36

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

NOTE.—Only those places are included which had not previously reported any of the above-named diseases, except yellow fever, during the current year. All reports of yellow fever are published currently.

A cumulative table showing the reported prevalence of these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday of each month.

Yellow Fever

Brazil—Amazonas State—Manacapuru.—On July 2, 1941, 1 death from yellow fever was reported in Manacapuru, Amazonas State, Brazil.

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