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THE CORRELATION BETWEEN NEUTRALIZING ANTIBODIES IN SERUM AGAINST INFLUENZA VIRUSES AND SUSCEPTIBILITY TO INFLUENZA IN MAN [1]

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There is now a considerable body of evidence *(1–8)* which indicates that the symptom-complex termed influenza is not a single disease entity but is instead a syndrome of diverse etiology. Except in the case of influenza A (*9*) nothing is known of the significance of neutralizing antibody levels against the viruses etiologically related to influenza. In this disease it has been suggested (*10–12*) that persons who possessed low antibody levels against influenza A virus were more susceptible than were persons who possessed high antibody levels. Recently it was reported (*3*) that in a group of normal persons whose antibody levels against this virus had been determined prior to the occurrence of an outbreak of influenza A, the attack rate for this disease was highest in the lowest antibody range and decreased progressively as antibody levels increased. This evidence indicated that in influenza A there was a correlation between low antibody levels and susceptibility as well as between high antibody levels and resistance to the disease. However, the data did not indicate that any concentration of neutralizing antibodies, however high, would assure complete immunity against influenza A.

In the case of influenza B (*5*), as well as in influenza of unknown cause (*8*), no evidence has as yet been adduced concerning the significance of antibody levels against either of the two known influenza viruses and susceptibility, or resistance, to these diseases.

The development of a quantitative neutralization technique (*13*) by which the concentration of antibodies against influenza A virus in a serum can be measured with reproducible results has permitted the study of a number of sera in different tests and direct comparisons between the results obtained. Since it has been shown (*14*) that a

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linear relationship exists between the quantity of virus neutralized and the quantity of serum used, it is possible to calculate the maximum quantity of virus which can be neutralized by a given serum. This quantity has been termed the neutralizing capacity, and it has been found that it is a constant value for a given serum irrespective of the amount of virus used in the neutralization test.

During the past 3 years serum has been obtained from a considerable number of normal individuals. During the same interval acute-phase and convalescent sera were obtained from a number of cases of influenza which occurred during epidemics in the same geographical areas. The neutralizing capacities of these sera against influenza A virus, influenza B virus, or both, were determined, and in each case of influenza an etiological diagnosis was established by means of appropriate laboratory tests.

It is the purpose of this paper to present the results of these studies and to show that there are correlations between the different levels of specific neutralizing antibodies and susceptibility, or resistance, to infection by the different agents etiologically related to influenza.

MATERIAL AND METHODS

Serum.—Serum was obtained from normal individuals who had not been exposed to an epidemic of influenza for at least 2 years. Serum was also obtained from cases of influenza during epidemics of this disease which occurred in 1939, 1940, and 1941. From patients with influenza serum was obtained either prior to the illness, or during the first few days of the disease, and again during convalescence, so that an etiological diagnosis could be established in each case. All cases from which acute-phase serum was taken later than the fifth day after clinical onset have been excluded from this analysis because of the possibility that after this interval an increase in antibodies might have resulted as a specific response to the infection itself. All sera were stored at 4° C.

Viruses.—The PR8 strain (*15*) of influenza A virus (*9*) and the Lee strain (*5*) of influenza B virus were used throughout this study. Both viruses were propagated in mouse lungs. Standard suspensions of infected mouse lungs were prepared as described previously (*13*) and were stored in a low temperature cabinet (*16*) at −76° C. between tests.

Neutralization tests.—Neutralization tests were carried out in a manner identical to that previously described (*12*). All sera prior to dilution were inactivated by heating to 56° C. for 30 minutes. Falling fourfold dilutions of serum in saline were mixed with a constant amount of the desired virus. The serum-virus mixtures were inoculated intranasally into groups of three or four lightly anesthetized albino mice

which were then observed for a period of 11 days. In parallel with each neutralization test a titration of the virus suspension used was carried out in a manner identical to that previously described (*13*). In order to determine the neutralizing capacity of each serum studied, it was necessary to cover the wide range of capacities from log 1.76 to log 6.96. It was found that the most efficient means of accomplishing this was to use between 310 and 3,100 fifty percent mortality doses of either virus against three or four serial dilutions of serum in the initial neutralization test. In those instances in which too much antibody was present to give an end point under these conditions, higher dilutions were tested subsequently against the larger quantity of virus. In those instances in which too little antibody was present to give an end point under these conditions, dilutions of the serum were tested subsequently against smaller quantities of virus. With some sera it was necessary to use between 10 and 30 fifty percent mortality doses of virus in order to obtain end points.

Calculation of neutralizing capacity.—The neutralizing capacity of each serum tested was calculated from the serum dilution end point and the quantity of virus used in the test by means of the equation (*14*)

$$\log b = y - (a \cdot \log x).$$

Both the serum dilution end points and the virus titration end points were calculated by the 50 percent end point method of Reed and Muench (*17*). As was stated in the preceding paper (*8*), it has been found that the linear relationship between the quantity of serum used and the quantity of virus neutralized was operative with influenza B virus just as it was with influenza A virus. Therefore, it was equally possible to calculate the desired neutralizing capacity whichever virus was used.

Determination of etiology of influenza.—Acute-phase and convalescent sera from each case of influenza were studied. In the great majority of cases the neutralizing capacities against influenza A virus, influenza B virus, or both, of the two serum specimens were determined. An increase during convalescence in neutralizing capacity against either virus of log 0.86 was taken to be a significant increase in antibodies, and therefore to indicate that infection by the homologous virus had occurred. This increase in neutralizing capacity corresponded to a fourfold increase in neutralizing titer. In the remaining cases the titers of complement-fixing antibodies against either influenza A virus, influenza B virus, or both of the acute-phase and convalescent sera, were determined by the methods described by Eaton and Rickard (*18*) and Francis (*6*). An increase of one dilution or more in the complement-fixing titer of the convalescent serum was considered to indicate a significant increase in antibodies and was, therefore, taken as evidence that infection by the homologous virus

had occurred. Cases in which a significant increase in antibodies against influenza A virus was demonstrated were designated influenza A. Cases in which a significant increase in antibodies against influenza B virus was demonstrated were designated influenza B. Cases in which no significant increase in antibodies against either virus was demonstrable were classified as influenza of unknown cause. For the purposes of this study these latter cases have been termed "influenza Y".

EXPERIMENTAL

Neutralizing antibodies against influenza A virus in normal individuals.—The neutralizing capacities against the PR8 strain of influenza A virus of serum obtained from a number of normal persons were determined by the method described above. So-called "standard neutralization titers" determined on the serum from 1,101 of these individuals have been reported previously (*3*). Neutralizing capacity ranges were chosen which permitted the grouping of various antibody levels in order to simplify the analysis. The ranges were purposely selected so as to correspond with certain "standard neutralization titer" ranges and thus to facilitate comparisons with earlier data (*3*, *19*). The number of individuals who possessed sera with neutralizing capacities in a given range was determined, and the frequency with which capacities in this range occurred among the whole group was calculated. The results are shown in table 1. It was found

TABLE 1.—*Distribution of neutralizing capacities against influenza A virus in serum of normal individuals, cases of influenza A, influenza B, and influenza "Y"*

Neutralizing capacity range against influenza A virus (log.)	Normal individuals		Cases of influenza A			Cases of influenza B			Cases of influenza "Y"		
	Number	Percent	Number	Percent	A/N ratio	Number	Percent	B/N ratio	Number	Percent	"Y"/N ratio
<2.63	243	18.4	72	23.2	1.28						
2.63 to 3.49	114	8.6	56	18.1	2.10	3	9.4	0.35	12	11.6	0.43
3.50 to 4.35	240	18.2	94	30.3	1.66	11	34.4	1.89	24	23.3	1.28
Combined					1.58			.97			.77
4.36 to 5.22	450	34.1	63	20.3	.59	11	34.4	1.01	33	32.0	.94
5.23 to 6.09	238	18.0	23	7.4	.41	7	21.9	1.22	34	33.0	1.82
6.10 to 6.96	36	2.7	2	.6	.22	0			0		
Total	1,321	100.0	310	100.0		32	100.0		103	100.0	

that 597 individuals, or 45.2 percent, of the group of 1,321 possessed sera with neutralizing capacities against this virus of log 4.35 or less. A random sample of 359, or 60.2 percent, of the sera from these individuals was tested against small quantities of virus as described above so as to obtain a reasonable approximation of the frequencies with which the three lowest neutralizing capacity ranges occurred. It was found that 40 percent, 19.1 percent, and 40.7 percent of these sera

had antibody levels in the ranges log 4.35 to 3.50, log 3.49 to 2.63, and log 2.62 or less, respectively. From these data the number of normal individuals with serum in the three lowest ranges was calculated. It will be noted that there were wide differences between the amounts of neutralizing antibodies against influenza A virus possessed by normal individuals. Neutralizing capacities in the range log 6.10 to 6.96 were, on the average, 20,000 times greater than those in the range log 2.62 or less. The largest number of individuals in one neutralizing capacity range occurred in the range log 4.36 to 5.22. Sera in this range were capable of neutralizing between 22,000 and 165,000 fifty percent mortality doses of influenza A virus per 0.05 cc. The frequency of antibody levels both above and below this range was found to diminish progressively, with the exception of the range log 2.62 or less in which there were more individuals than might be expected on the basis of a normal distribution curve. It should be pointed out that this range includes all neutralizing capacities from 0 to log 2.62, and therefore that it is three times broader than any of the higher ranges.

Neutralizing antibodies against influenza A virus in influenza A.— The neutralizing capacities against the PR8 strain of influenza A virus of serum obtained either prior to or during the first days of the illness from a number of patients with influenza A were determined. An etiological diagnosis was established in each case by the methods described above. So-called "standard neutralization titers" for the sera of 59 of these cases have been reported previously (*3*). The number of cases with sera in a given neutralizing capacity range was determined, and the frequency with which each range occurred was calculated. The results are shown in table 1. It was found that 128, or 41.3 percent, of the 310 cases possessed sera with neutralizing capacities against influenza A virus of log 3.49 or less. Sera from a random sample of 71, or 55.5 percent, of these cases were tested against smaller quantities of virus as described above in order to obtain the approximate frequencies of occurrence of the two low ranges. It was found that 43.7 and 56.3 percent of these sera had antibody levels in the ranges log 3.49 to 2.63 and log 2.62 or less, respectively. From these data the number of cases in the two low ranges was calculated. It will be observed that the largest number of cases of influenza A in one neutralizing capacity range occurred in the range log 4.35 to 3.50 and that this range was next lower from that in which there was the highest frequency of normal individuals. The frequency with which cases of influenza A were encountered with antibody levels above this range was found to diminish progressively. It is apparent that the distribution of antibody levels among cases of

influenza A was distinctly different from that among normal individuals. The A/N ratios shown in table 1 serve to express this difference in a single term. These ratios were calculated by dividing the frequency with which a given neutralizing capacity range was encountered in the serum of cases of influenza A by the frequency with which the same range was found in the serum of normal individuals. It seems apparent that had influenza A occurred irrespective of the neutralizing capacities against the homologous virus, then, in samples of this size, the A/N ratios should have approximated unity. On the other hand, if the level of neutralizing antibodies against influenza A virus were one of the variables related to the occurrence of influenza A, it would be expected that in the low antibody ranges the A/N ratios would be greater than 1.0, while in the high antibody ranges the ratios should be less than 1.0. The progressive increase in the A/N ratios from 0.22 in the highest range to 2.10 in the next to the lowest range indicated that, in general, the lower the antibody level against the homologous virus of an individual's serum, the more likely was the occurrence of influenza A.

Neutralizing antibodies against influenza A virus in influenza B.—The neutralizing capacities against the PR8 strain of influenza A virus of serum obtained during the first days of illness from a number of patients with influenza B were determined. An etiological diagnosis was established in each case by the methods described above. The number of cases in each neutralizing capacity range was determined and the frequency with which each range occurred was calculated. The results are shown in table 1. Although only 32 cases of influenza B were available for this analysis, it is apparent that the frequency with which various antibody levels against influenza A virus occurred among them was not very different from the incidence of the same levels among normal persons. The ratios B/N serve to express this relationship in one figure and were calculated in a manner identical to that used for the determination of A/N ratios. The ratios 0.35 and 1.89 were undoubtedly the result of the small size of the samples, since when the frequencies of cases of influenza B in both low ranges are combined and compared to the combined normal frequencies in the same ranges the B/N ratio becomes 0.97. It seems obvious that high antibody levels against influenza A virus did not tend to diminish the likelihood of the occurrence of influenza B. In fact, influenza B appears to have occurred without regard to the concentration of antibodies against influenza A virus.

Neutralizing antibodies against influenza A virus in influenza "Y".—The neutralizing capacities against the PR8 strain of influenza A virus of serum obtained during the first days of illness from a number of patients with influenza "Y" were determined. As was stated above,

cases were classified as influenza "Y" only when it was found that no significant increases in antibodies against influenza A and influenza B viruses were demonstrable during convalescence. The number of cases in each neutralizing capacity range was determined and the frequency with which each range occurred was calculated. The results are shown in table 1. To express the relationship between the rfequencies of various antibody levels among normal individuals and cases of influenza "Y" in one figure, "Y"/N ratios have been calculated in a manner identical to that used for A/N ratios. It is apparent that the "Y"/N ratio was the lowest in the lowest antibody ranges and highest in the highest range in which cases occurred. If the frequencies in the two low ranges are combined and compared to the com-

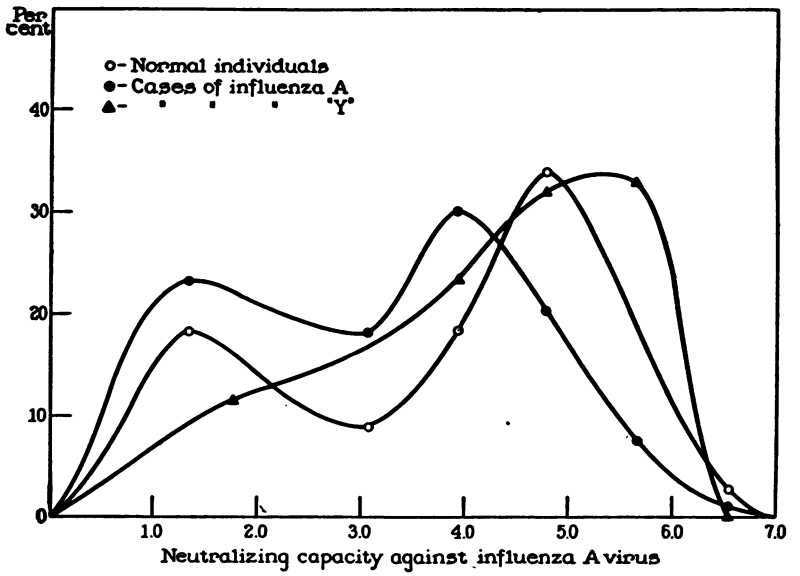

FIGURE 1.—The distribution of neutralizing antibody levels against influenza A virus among 1,321 normal individuals, 310 cases of influenza A, and 103 cases of influenza of unknown cause ("Y").

bined normal frequencies in the same ranges, the "Y"/N ratio becomes 0.77. Under these circumstances it will be noted that the ratios progressively increased as antibody levels became higher. This indicated in general that the greater the concentration of antibodies against influenza A virus possessed by an individual the more likely was the occurrence of influenza "Y". It will be recalled that this finding is the reverse of what was observed among cases of influenza A.

The results of the studies of neutralizing antibodies against influenza A virus are shown graphically in figure 1. The percentage incidence of normal individuals, cases of influenza A, and cases of influenza "Y" have been plotted against the neutralizing capacity ranges. Smooth curves which appeared best to fit the points have

been drawn through them. The tendency for cases of influenza A to occur predominantly among individuals with low antibody levels and for cases of influenza "Y" to occur chiefly among individuals with high antibody levels is clearly shown. In figure 2 are presented the frequency ratios which express the proportional incidences of influenza A, influenza B, and influenza "Y" relative to the distribution of antibody levels among normal individuals. The calculated

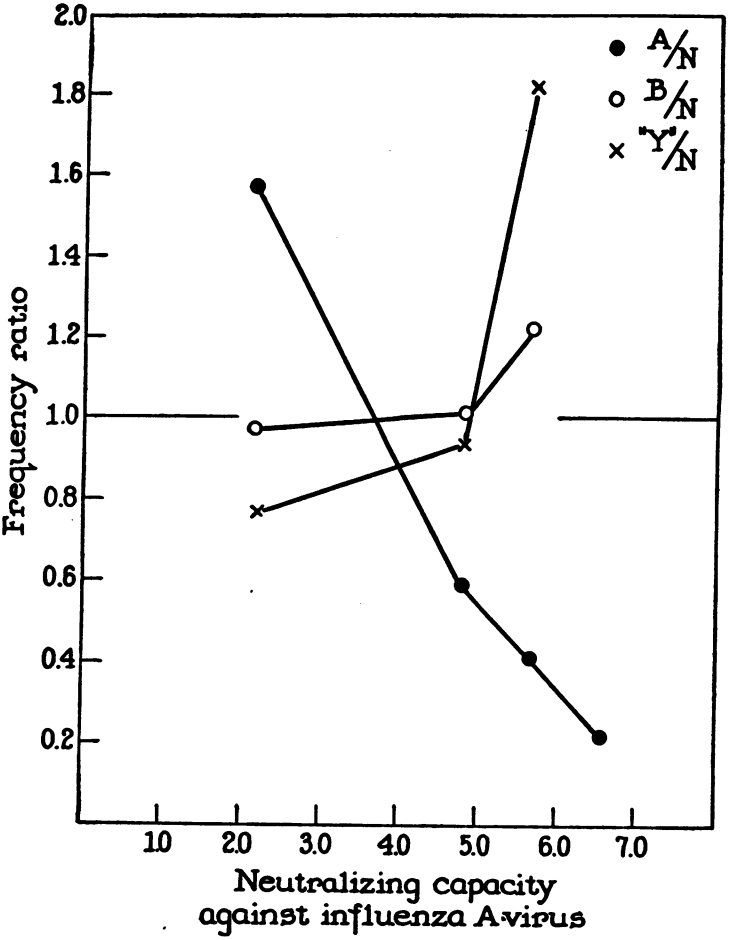

FIGURE 2.—The frequency ratios of neutralizing antibody levels against influenza A virus among cases of influenza A, influenza B, and influenza of unknown cause ("Y") relative to normal individuals.

ratios have been plotted against the neutralizing capacity ranges. The points have been connected by straight lines to assist in the interpretation of results.

Neutralizing antibodies against influenza B virus in clinical influenza.—The neutralizing capacities against the Lee strain of influenza B virus of serum obtained during the first days of illness from a number of cases of clinical influenza were determined. Although an

etiological diagnosis was subsequently established for each case, this group of cases was first analyzed without regard to etiology. Since it has not yet been feasible to determine the antibody levels against influenza B virus of serum from a representative sample of normal individuals, the results obtained in this group of cases were used in lieu of these data. Neutralizing capacity ranges identical with those used in the analysis of antibodies against influenza A virus were chosen in order that comparisons might be facilitated. The number of cases in a given range was determined, and the frequency with which each range occurred was calculated. The results are presented in table 2. It will be observed that there were wide differences in the amounts of neutralizing antibodies against influenza B virus possessed by these individuals. Some cases had neutralizing capacities at least 1,000 times higher than others. The largest number of cases possessed sera in the range log 3.50 to 4.35. Sera in this range were capable of neutralizing between 3,100 and 22,000 fifty percent mortality doses of influenza B virus per 0.05 cc. The frequency of antibody levels below this range diminished gradually. Above this range only 6 cases of influenza were encountered.

TABLE 2.—*Distribution of neutralizing capacities against influenza B virus in serum of cases of clinical influenza, influenza B, influenza A, and influenza "Y"*

Neutralizing capacity range against influenza B virus (log.)	Cases of clinical influenza, all varieties		Cases of influenza B			Cases of influenza A			Cases of influenza "Y"		
	Number	Percent	Number	Percent	B/T ratio	Number	Percent	A/T ratio	Number	Percent	"Y"/T ratio
< 2.63	30	21.3	23	53.5	2.51	3	8.6	0.40	2	4.5	0.21
2.63 to 3.49	50	35.5	11	25.6	0.72	16	45.7	1.29	14	31.8	0.90
Combined					1.39			0.96			0.64
3.50 to 4.35	55	39.0	10	23.3	0.60	14	40.0	1.03	24	54.6	1.40
4.36 to 5.22	3	2.1	0			1	2.8	1.32	2	4.5	2.14
5.23 to 6.09	3	2.1	0			1	2.8	1.32	2	4.5	2.14
Total	141	100.0	44	100.0		35	100.0		44	100.0	

Neutralizing antibodies against influenza B virus in influenza B.—The neutralizing capacities against the Lee strain of influenza B virus of acute-phase sera from a number of cases of influenza B were determined. An etiological diagnosis was established by the methods described above. The number of cases in the various ranges was determined, and the frequency of each range calculated. The results are shown in table 2. It will be seen that the largest number of cases occurred in the lowest range and that no cases were found which possessed antibody levels in the two upper ranges. It seems apparent that the distribution of antibody levels among cases of influenza B was different from that among the whole group of cases of clinical influenza even though the former cases were included in the group.

The B/T ratios presented in table 2 serve to express this difference simply. These ratios were calculated by dividing the frequency with which a given neutralizing capacity range was found in the serum of cases of influenza B by the frequency with which the same range was encountered in the serum from the whole group of cases. The progressive increase in the B/T ratios from 0 in the highest range to 2.51 in the lowest range indicated that in this group of cases influenza B occurred with increasing frequency as antibody levels against the homologous virus decreased.

Neutralizing antibodies against influenza B virus in influenza A.— The neutralizing capacities against the Lee strain of influenza B virus of acute-phase sera from a number of cases of influenza A were determined. An etiological diagnosis was established as described above. The number of cases in the various neutralizing capacity ranges was determined and the frequency of each range calculated. The results are presented in table 2. Although the number of cases of influenza A studied in this manner was not large, it is apparent that the distribution of antibodies among them was similar to the distribution in the whole group. The ratios A/T serve to demonstrate this relationship and were calculated in a manner identical to the B/T ratios. With the exception of the ratio 0.40 in the lowest range, the A/T ratios in the lower three ranges were not far from unity. This low ratio was undoubtedly seriously influenced by the fact that of the 30 cases in the lowest neutralizing capacity range 23 were influenza B. If the frequencies of cases of influenza A in both low ranges are combined and compared to the combined frequencies among the whole group in the same ranges, the A/T ratio becomes 0.96. It seems obvious that the various antibody levels against influenza B virus were unrelated to the occurrence of influenza A.

Neutralizing antibodies against influenza B virus in influenza "Y".— The neutralizing capacities against the Lee strain of influenza B virus of acute-phase sera from a number of cases of influenza "Y" were determined. Only those cases in which no significant increases in antibodies against influenza A and B viruses were demonstrable during convalescence were classified as influenza "Y." The number of cases in the various neutralizing capacity ranges was determined and the frequency of each range calculated. The results are shown in table 2. It will be observed that the distribution of antibody levels among these cases was different from that encountered in the whole group. The differences are more clearly evident in the "Y"/T ratios which were calculated in a manner identical to the B/T ratios. In the lower three ranges the "Y"/T ratios progressively increased as antibody levels increased. The ratio 0.21 was probably a direct result of the high proportion of influenza B among the total cases in

the lowest range. If the combined frequencies for influenza "Y" in the two lowest ranges are compared with the combined frequencies in the same ranges for the whole group, the "Y"/T ratio becomes 0.64. Under these conditions there was still an indication that as antibody levels against influenza B virus increased the occurrence of influenza "Y" increased. It will be noted that this is the reverse of what was observed in influenza B.

The results of the studies of neutralizing antibodies against influenza B virus are shown graphically in figure 3. The percentage incidence

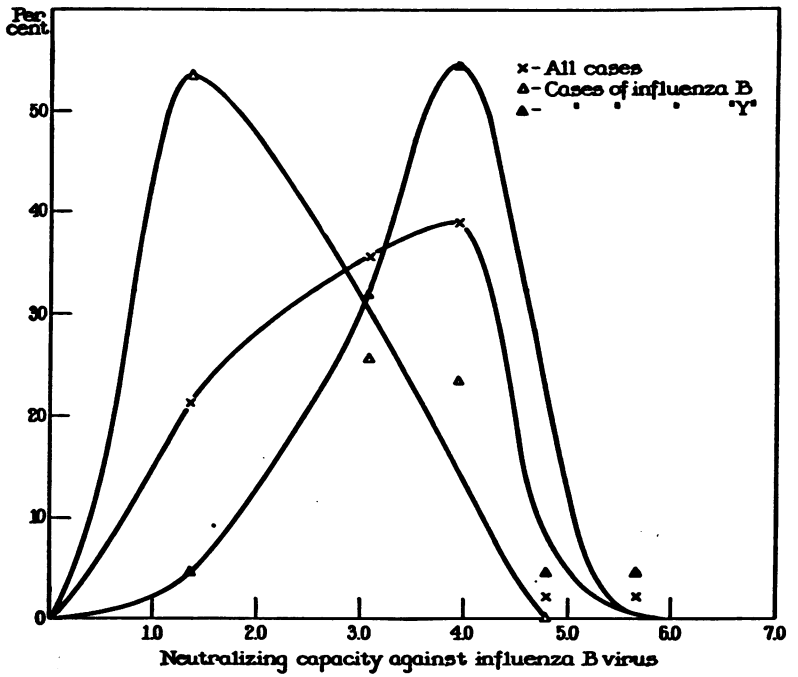

FIGURE 3.—The distribution of neutralizing antibody levels against influenza B virus among 141 cases of clinical influenza irrespective of etiology, 44 cases of influenza B, and 44 cases of influenza of unknown cause ("Y").

of all cases studied, cases of influenza B and cases of influenza "Y," respectively, have been plotted against the neutralizing capacity ranges. Smooth curves which appeared to fit the points well have been drawn. The increased incidence of cases of influenza B among individuals with low antibody levels and of cases of influenza "Y" among those with high antibody levels is evident. In figure 4 are presented the frequency ratios which express the proportional incidences of influenza B, influenza A, and influenza "Y" relative to the distribution of antibody levels among all cases investigated. The calculated ratios have been plotted against the neutralizing capacity ranges. The points have been joined by straight lines to facilitate an appraisal of the trends observed.

DISCUSSION

The variables which are responsible for susceptibility or immunity to influenza in human beings are of obvious importance. A full knowledge of them might be expected to indicate those which were of most significance in determining resistance to these diseases. This

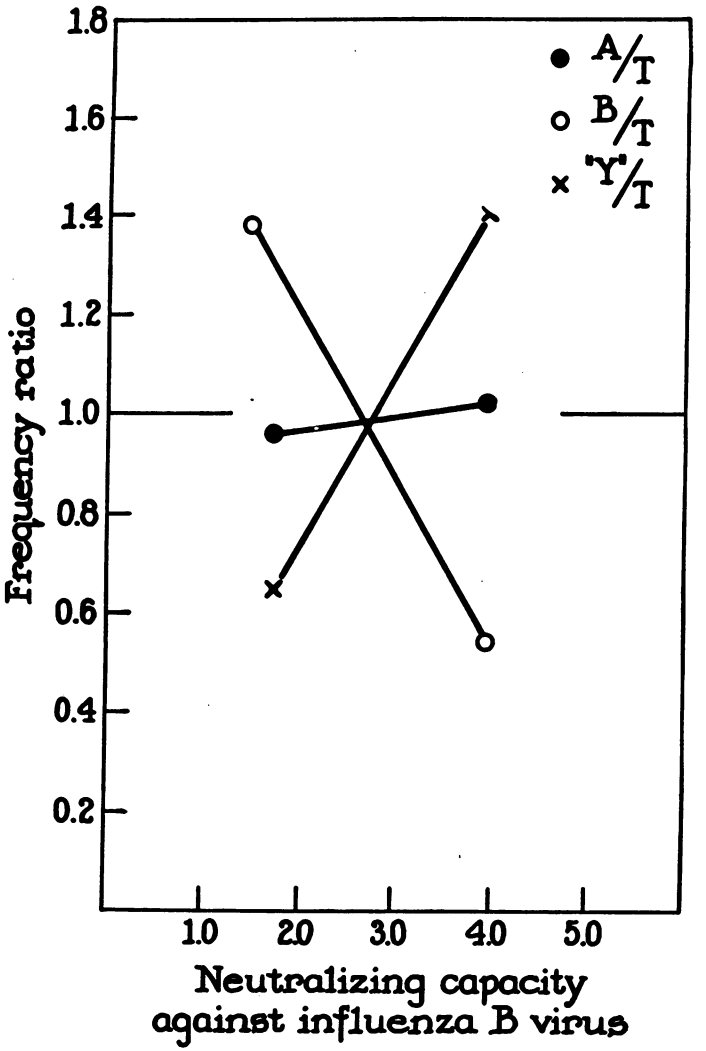

FIGURE 4.—The frequency ratios of neutralizing antibody levels against influenza B virus among cases of influenza A, influenza B, and influenza of unknown cause ("Y") relative to all cases studied.

information should be of great value in attempts to increase immunity to the infection since the method of preference would reasonably be that one which most augmented the more important factor or factors.

At the present time there exists but little information as to the relative importance of the various factors which may be related to

immunity or susceptibility to influenza. The variable most readily measurable and therefore that which has been most studied is serum antibodies specifically directed against the etiological agents. Whether neutralizing antibodies against influenza A virus possessed by normal individuals are merely a partial reflection of immunity to influenza A or are directly responsible for that state has concerned a number of investigators.

A direct assessment of immunity to influenza A virus in man has been fraught with difficulties. It has become apparent that laboratory strains of the virus may possess very different degrees of pathogenicity for human beings, depending to a considerable extent upon the species in which they have been propagated and the number of passages to which they have been subjected. Andrewes, Laidlaw, and Smith (*20*) failed to infect volunteers who possessed antibodies against the agent with virus propagated in ferrets. It was shown by Burnet and Lush (*21*) and by Francis (*22*) that virus propagated for long periods in chick embryo tissue did not produce influenza after intranasal instillation in human beings even though some individuals tested possessed little or no antibodies against the agent. However, Smorodintsev et al. (*23*) reported the production of influenza in some volunteers with virus propagated in mice, and Burnet and Foley (*24*) showed that a strain recently recovered from a case of influenza A and passed only a few times in the chick embryo produced influenza in 3 of 15 inoculated individuals. In both these latter reports it was demonstrated that volunteers who contracted the experimentally induced disease had low levels of neutralizing antibodies against influenza A virus, whereas those who did not develop influenza possessed higher antibody levels. These results suggested that the level of neutralizing antibodies was of significance in determining susceptibility or immunity to influenza A in man. But the conditions under which the experimental disease was produced and the relatively large quantities of virus suspensions used seem so different from conditions encountered in the natural epidemic disease as to make comparisons between these two conditions hazardous. On the basis of studies of neutralizing antibody titers in the serum of patients with influenza A and persons in contact with these cases, Francis et al. (*11*) suggested that there was a critical level of antibodies between susceptibility and immunity to the disease. However, Rickard et al. (*3*) found that, although persons possessing serum in any of the various standard neutralizing titer ranges might contract influenza A, individuals in the lowest titer range showed attack rates considerably greater than those in the higher titer ranges.

The results presented in this paper suggest that the level of specific neutralizing antibodies against the homologous virus is one important factor in immunity to both influenza A and influenza B. That

neutralizing antibodies are not the only factor of importance in determining whether a given individual will contract one or the other disease entity in an epidemic is also evident. Even in the highest neutralizing capacity ranges encountered among normal individuals some cases of influenza occurred, although these were uncommon. Since these higher antibody levels were equal to or greater than those of numerous persons recently convalescent from either influenza A or influenza B, it seems unreasonable to assume that these concentrations of antibodies were less significant as regards immunity than those which followed these diseases themselves.

It is a surprising fact that occasional human beings may possess serum, each cubic centimeter of which is capable of neutralizing well over 20 million mouse lethal doses of influenza A virus, and still be susceptible to influenza A. It seems possible that the peculiar anatomy of the upper respiratory tract may prevent intimate contact between virus and circulating antibodies and thus permit the infectious agent to establish itself in some individuals no matter what concentration of specific antibodies may be present in the blood within adjacent capillaries. That this is not generally the case is indicated by the fact that there was a distinct tendency for both influenza A and influenza B to occur most commonly in individuals who possessed during the acute phase of their disease relatively low levels of antibodies against the homologous virus.

If, as is assumed, influenza is actually transmitted from one person to another by means of virus-containing droplets, it seems possible that individual exposure in an epidemic may be extremely variable, and whereas one person may come into contact with a small quantity of the virus another may inhale a large amount. Under these circumstances the variable quantity of the infecting agent might be partly responsible for the apparent lack of a closer correlation between immunological findings and immunity to the disease.

Possibly the concentration of the virus-inactivating agent described by Burnet, Lush, and Jackson (*25*), as well as by Francis (*26*), in the nasal secretions may also be one of the variables related to immunity or susceptibility to influenza A. As yet there does not appear to be any direct evidence available on this interesting hypothesis. Recent experiments by Francis (*27*) raise the possibility that this agent may be similar, if not identical, to neutralizing antibody. Whether the substance present in nasal secretions is also capable of inactivating influenza B virus does not seem to have been determined as yet.

The available experimental evidence (*4–7*) indicates that influenza A virus and influenza B virus do not possess a common antigenic component. Consequently, it would not be expected that high antibody levels against influenza A virus would be correlated with

immunity to influenza B or that high antibody levels against influenza B virus would be correlated with immunity to influenza A. As might have been anticipated, the distribution of antibody levels against influenza A virus of cases with influenza B was similar to that of the normal population. Conversely, the distribution of antibody levels against influenza B virus of cases with influenza A appeared to be random though in this instance the evidence is less conclusive since the normal distribution of antibodies against this agent is not known.

The results of the study of antibodies against both influenza A virus and influenza B virus in cases of influenza of unknown cause, i. e., influenza "Y," require some comment. If it is assumed that influenza "Y" is a group of etiological entities associated with infection by the hypothetical agents influenza "C" virus, "D" virus, etc., (*9*), and that each of these agents is antigenically distinct from both influenza A and B viruses, it would be reasonable to expect that there should be no correlation, either positive or negative, between antibody levels against these latter viruses and the occurrence of influenza "Y." However, it was found, very surprisingly, that the distribution of antibody levels was not entirely random in cases of influenza "Y" and this disease appeared to occur with increasing frequency as the concentration of antibodies against either of the two known influenza viruses increased.

An attempt to explain these wholly unexpected negative correlations is hazardous in the absence of direct evidence concerning the etiology of influenza "Y." At the present time it seems wise merely to record these observations and to offer no tentative hypothesis which might serve as a logical explanation for them.

SUMMARY

The level of neutralizing antibodies in the serum against the homologous virus is an important factor in determining susceptibility or resistance to influenza A and to influenza B in human beings. However, high antibody levels against influenza A virus do not diminish the frequency of influenza B nor do high antibody levels against influenza B virus reduce the incidence of influenza A. Influenza of unknown cause appears to occur with somewhat increased frequency among individuals who possess considerable concentrations of antibodies against both known influenza viruses.

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DIURNAL VARIATION OF URINARY LEAD EXCRETION[1]

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INTRODUCTION

During the latter part of 1937, when methods for the collection and preservation of blood and urine were being investigated in this laboratory, the importance of the time of collection of single urine specimens for lead determinations was not generally realized. Accordingly, a study was begun in this laboratory to determine whether or not all urine samples collected from one individual during the day would show the same lead concentration.

Following the discovery of a marked diurnal variation in this individual the work was repeated on the same subject at a different time of year and later extended to include 6 other persons.

DIURNAL VARIATION

It has long been known that, for the common constituents, the composition of urine excreted by a given individual may fluctuate considerably during a 24-hour period. Nearly a century ago Bence-Jones was among the first (*1*) to observe a decrease in the acidity of urine

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

following meals. This author also made observations regarding variations in phosphate and uric acid excretion and in a later publication (*2*) referred to the diurnal variation in the acidity of the urine. Roberts (*3*) in 1859 was apparently the first (*4*) to use the term "alkaline tide" for the decrease in the acidity of urine after meals. Both authors referred to titratable acidity rather than to changes in pH.

Although common agreement has not been reached regarding the causes of this phenomenon, the widespread existence of diurnal variation has been shown for a number of important urinary constituents, such as phosphate (*5*), urea (*6*), uric acid (*7*), and chloride (*8*).

Quite apart from the theoretical explanations, the practical result of the recognition of this change in composition has been the common use of morning or 24-hour specimens rather than single short-time specimens in order to minimize this variability and to secure a more representative sample.

When the determination of the lead content of urine specimens first became a common procedure comparatively large volumes were needed in order to measure the lead quantitatively. Analyses were therefore usually confined to samples collected for 24 hours or longer.

With the refinement of analytical methods the sensitivity increased to such an extent that smaller quantities of urine could be used. Indeed, with the development of the dithizone method for lead detection, the quantities could be reduced from 1,000 or 2,000 cc. to 100 or 200 cc. Use of even smaller amounts was advocated by some (*9*, *25*).

This reduction in sample size had an obvious advantage as far as time and effort in the collection of samples were concerned. Usually a single voiding sufficed to give enough material for one or more analyses. In industrial studies it is usually impracticable to collect 24-hour specimens on a large group of individuals. This is due to several factors such as danger of contamination of the samples, the inconvenience to the subjects, and the uncertainty that the entire 24-hour output had been saved.

For these reasons the common method has been to collect single specimens at the time of day most convenient for the subject, usually at the time of the physical examination. This was the plan adopted in the study of the lead storage battery industry (*10*).

On the other hand, the wide variation in daily urine output for different individuals is a well known fact. It is also recognized that children and adults differ in regard to urine volumes (*11*, *12*). Even an average value for males may not hold for females (*13*). The total volume depends on the temperature, humidity, muscular effort, perspiration, and water consumption, as well as other physiological and psychic factors.

With essentially normal individuals this quantity may commonly vary from 800–1,500 cc. (*14*) to 1,000–1,800 cc. (*12*) daily, and urine volumes for a given individual may also vary widely from day to day and from hour to hour (*14*). In order to increase diagnostic significance, therefore, samples taken over large time intervals are desirable, since interpretations made on the basis of analyses of single specimens may be faulty. Information concerning the total output of lead during a 24-hour period is consequently of more value than the concentration for a single specimen in terms of milligrams of lead per liter.

In the collection of urine specimens for the lead arsenate spray residue study (*15*) a compromise was effected. Since it appeared that the first morning specimen was a more representative sample of the day's output, because it was collected over a longer period of time, it was decided to take morning specimens in most cases and to supplement these with some 24-hour and short-time specimens.

The purpose of the following investigation was to secure information regarding the range in composition of urine specimens collected from given individuals during the entire day. While the chief interest was in the lead content, data about other important urinary constituents, such as phosphorus and arsenic, were also sought. In addition, it was hoped to determine whether any variation in the blood occurred simultaneously with or independently of urine changes.

EXPERIMENTAL PROCEDURE

Four healthy adult male orchardists having 25 to 30 years of orchard experience were chosen from the Wenatchee group of individuals included in the lead arsenate spray residue study (*15*). In addition, three healthy adult males, classed as consumers, having no known exposure to lead arsenate, were selected from the personnel of the laboratories of the Division of Industrial Hygiene, National Institute of Health.

From these seven individuals the total urinary output was collected in separate lead- and arsenic-free containers at each voiding during 3- or 4-day periods and a total of 189 specimens was secured. The same procedure was used as that employed in the earlier studies (*10*, *15*). In addition, blood specimens were taken three times a day on two alternate days from two of the consumers. The number of urine specimens collected from any one person during a 24-hour period varied from 4 to 10, the average for all subjects being 6.4 specimens per day. Since no attempt was made to collect the specimens at regular periods, the time interval between samples varied greatly, these intervals ranging from three-fourths of an hour to 10 hours, with an average of 3.9 hours for a 24-hour period.

Data were obtained on four series for consumers and three for orchardists; 100 cc. specimens of urine were taken for lead determination

whenever possible. For smaller samples urine from two adjacent intervals was combined. The pH and the volume were determined on all and specific gravity and phosphate measurements on all but two series. The importance of chloride and calcium determinations was not sufficient to justify making a larger number of these measurements. Where sufficient volume permitted, arsenic determinations were also made.[2]

From the analytical data could be calculated urinary lead in terms of concentration (in milligrams per liter), rate of excretion (in micrograms per hour), and total quantity (in milligrams). Similar data were obtained for urinary phosphate measurements. By successively plotting these quantities, one at a time, against other factors, such as time, pH, specific gravity, water output, etc., it was possible to study the relation between these various factors.[1]

Space does not permit giving the individual values for the thousand-odd determinations made during this study. Instead, most of these have been incorporated, together with other calculated quantities, in a series of seven figures showing in graphic form the variation of these various measurements with time (figs. 1–6).

This was done for a given person by plotting a set of values, such as urinary lead concentrations, against the time of day and connecting these points with straight lines. One graph was made for each kind of measurement. It will be noted that there are three parts to each figure, dealing with concentration values, rates of excretion, and total amounts (output). Specific gravity and pH values are included in the section on concentrations since these values are related to the salt concentration and hydrogen-ion concentration, respectively. Each figure, therefore, summarizes the data for one of the experimental subjects.

Table 1 indicates some of the information regarding the experiment and relates the figures to the corresponding subjects.

TABLE 1.—*Information concerning experimental subjects*

Subject No.	Figure in which data is shown	Class of individuals	Date of starting experiment	Location of subject	Period of experiment (days)
1A	1A	Consumers (with no known exposure to lead arsenate).	Aug. 24, 1937	Washington, D. C.	3
1B	1B		Oct. 11, 1938	do	4
2	2		Mar. 25, 1940	do	3
3	3		do	do	3
4	4	Orchardists (with some exposure to lead arsenate).	Jan. 16, 1939	Wenatchee, Wash.	3
5	5		Dec. 16, 1938	do	3
6	6		Feb. 6, 1939	do	3

[1] Lead was determined by a photometric dithizone method (*10, 15*), arsenic by the Gutzeit method (*10, 15*), phosphate by a modification of the Leconte uranium acetate method (*16, 17*), chloride by the Arnold modification of the Volhard procedure (*18, 19*), and calcium by titration with potassium permanganate based on McCrudden's method (*20, 21*). The pH of urine specimens was determined colorimetrically (*10*).

Inspection of the graphs has yielded much valuable information. From such considerations the most significant results will be discussed.[3]

VARIATION OF URINARY LEAD CONCENTRATIONS

The first important point disclosed was that for all of the seven individuals studied the urinary lead concentration of single specimens

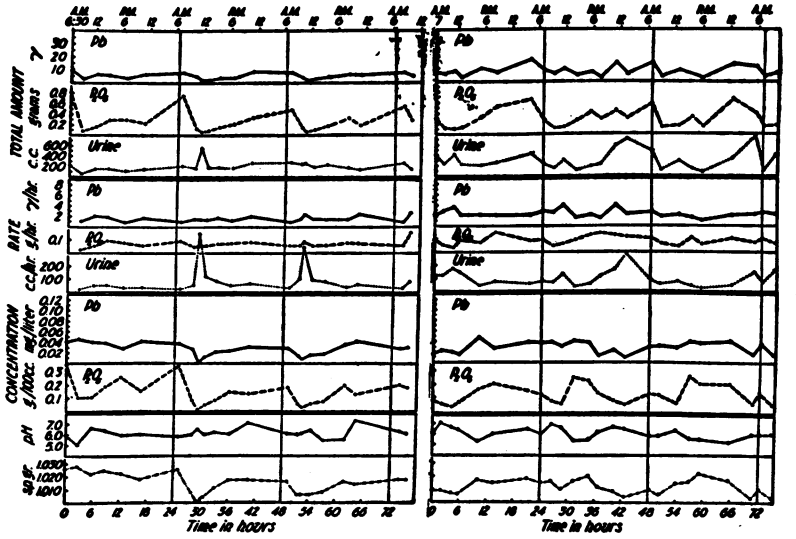

FIGURE 3.—Subject 3.

FIGURE 2.—Subject 2.

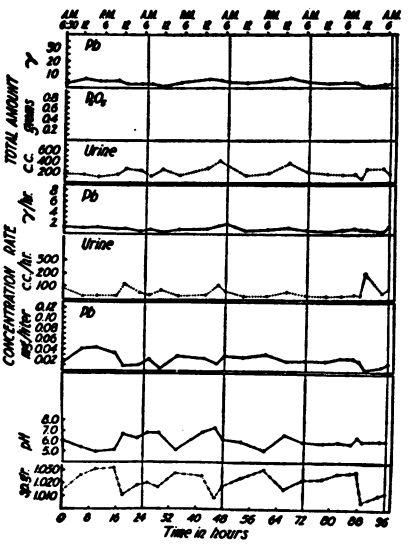

FIGURE 1B.—Subject 1B.

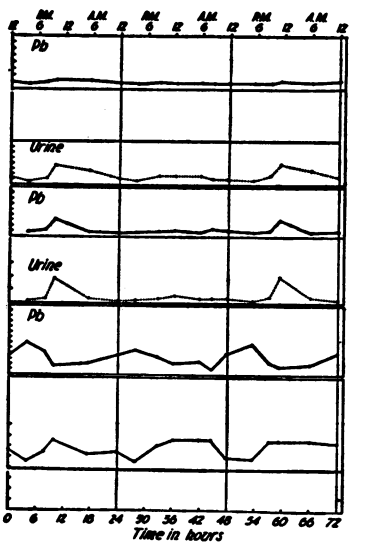

FIGURE 1A.—Subject 1A.

Urinary diurnal variation for 3 laboratory subjects.

varied greatly during the 24 hours of the day. During the 3- or 4-day periods the consumers had a range of 0.003 to 0.060 mg. per liter and

[3] In figures 1–6 corresponding graphs will be discussed in order reading from the bottom upward.

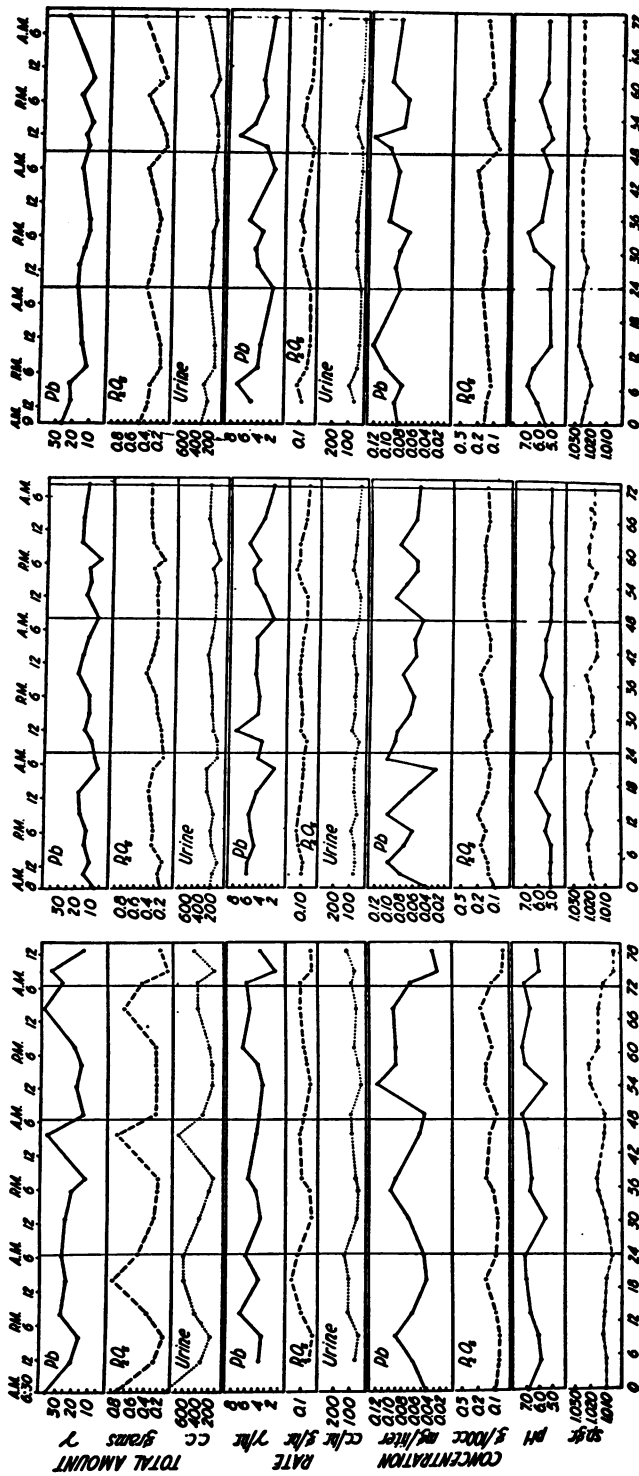

FIGURE 6.—Subject 6.

FIGURE 5.—Subject 5.

Urinary diurnal variation for 3 orchardists.

FIGURE 4.—Subject 4.

the orchardists a range of 0.025 to 0.124 mg. per liter. The greatest variation in a single day was from 0.017 to 0.060 mg. per liter for a consumer and from 0.025 to 0.101 for an orchardist.

Analyses of duplicate 100 cc. samples indicated a high degree of reproducibility for the lead determinations, usually within ± 0.003 mg. per liter. This clearly showed that the variation which was taking place was much greater than the experimental error of the determination.

The cyclic nature of the curves was evident and the recurrence of high and low points at approximately the same time of day was noted. (This is especially true in fig. 1A.) However, occasional minor peaks and troughs broke this regularity in nearly all of the subjects. Ninety-five percent of the time a peak concentration was found to occur between 4 p. m. and midnight, the average time being 7 p. m. No particular regularity was discovered for the other high points. While minimal values for a given individual showed considerable regularity there was no uniformity in time of such occurrences for the whole group since they were found throughout the 24 hours. It is also of interest to note that the variations in lead concentrations for individuals with low lead output were less than for those with higher lead levels.

A second finding was the inverse correspondence between these lead concentrations and pH values of the urine. This was most evident in the first case studied (fig. 1A) in which the most acid urines (those with lowest pH values) occurred at the times of maximal lead concentrations (4–6 p. m.).

Very little correspondence was noted between lead concentrations and corresponding phosphate concentration values (calculated as P_2O_5) and little between the latter and corresponding pH values.

The most pronounced relation was found for pH and specific gravity values. This inverse correspondence was noted particularly with the first subject (fig. 1B). It is likewise of interest to note the general parallelism for the lead concentration and specific gravity curves for this same person. Finally, the general inverse correspondence between rates of urine excretion and specific gravity values was evident in all the subjects, but particularly so for subject 1B.

VARIATION IN RATE OF URINARY LEAD EXCRETION

For all of the individuals studied a great variation in rate of urinary lead excretion (expressed in micrograms of lead per hour) was found. Table 2 shows the extreme values for the rates of each individual for each day of the experiment. For comparison, the extreme values are also given for concentration values for the same persons during the experimental period. The two sets of values do not necessarily

correspond to the same samples since concentration and rate are not directly related. For example, a specimen with a minimum concentration value would not necessarily show the minimum rate.

The rates for consumers ranged from 0.3 to 4.1 micrograms per hour and for orchardists from 1.8 to 7.8 micrograms per hour, the average rates for the whole period being 1.5 and 4.6 micrograms of lead per hour for consumers and orchardists, respectively.

TABLE 2.—*Daily variation in concentration and rate of urinary lead excretion for each individual during 3- or 4-day periods*

Subject No.	Range in urinary lead concentration (milligrams per liter)				Range in urinary lead rate (micrograms per hour)			
	First day	Second day	Third day	Fourth day	First day	Second day	Third day	Fourth day
1A	0.017	0.010	0.015	----------	0.7	0.8	0.8	----------
	.060	.046	.058	----------	3.2	1.5	3.0	----------
1B	.009	.004	.019	0.004	.5	.3	.6	0.4
	.044	.029	.032	.026	1.2	1.8	1.2	1.3
2	.015	.008	.015	----------	2.1	1.5	1.1	----------
	.048	.041	.041	----------	3.6	4.1	2.6	----------
3	.028	.003	.007	----------	.9	.9	.8	----------
	.046	.032	.041	----------	2.1	2.0	2.4	----------
4	.076	.066	.072	----------	1.8	1.8	2.3	----------
	.122	.098	.124	----------	7.2	5.6	7.2	----------
5	.025	.045	.053	----------	1.8	2.3	2.4	----------
	.101	.089	.090	----------	6.0	7.8	6.3	----------
6	.040	.043	.067	----------	3.6	3.8	3.6	----------
	.088	.097	.117	----------	7.0	5.9	6.7	----------

The graphs in figures 1–6 showing the variations in rate of lead output do not support the contention of Barnes (*22*) regarding the essential constancy of rates of lead excretion for any given individual.

It is evident from the data in table 2 that attempts made to judge the extent of lead absorption in terms of how much lead is being excreted per hour may lead to erroneous conclusions when based on short-time samples. Nor is it safe to make individual comparisons of urinary lead concentrations on single specimens unless additional information is at hand.

For several of the subjects the rate of lead excretion (in micrograms per hour) was directly related to the rate of urine excretion (in cubic centimeters per hour) for those samples in which the specific gravity was greater than 1.010. Also, marked water diuresis did not greatly increase the rate of lead excretion nor the total amount.

This relationship is shown for the various subjects in figure 7, in which the urinary lead rates are plotted against rates of urine excretion. The lines shown are lines of regression obtained by the least square method for points corresponding to samples with specific gravity values of 1.011 and over. The limited scattering of the values can

be seen to hold quite generally except for the values with low specific gravities.

A similarity in form of the phosphate rate curves and urinary rate curves was noted. This was especially marked in figure 6. It is possible that the same influences which affect the excretion of lead also control the excretion of phosphorus.

The rate of urine excretion was found to vary widely. The two pronounced humps in the curve of urine excretion in figure 3 were caused by the subject deliberately drinking considerable quantities of water.

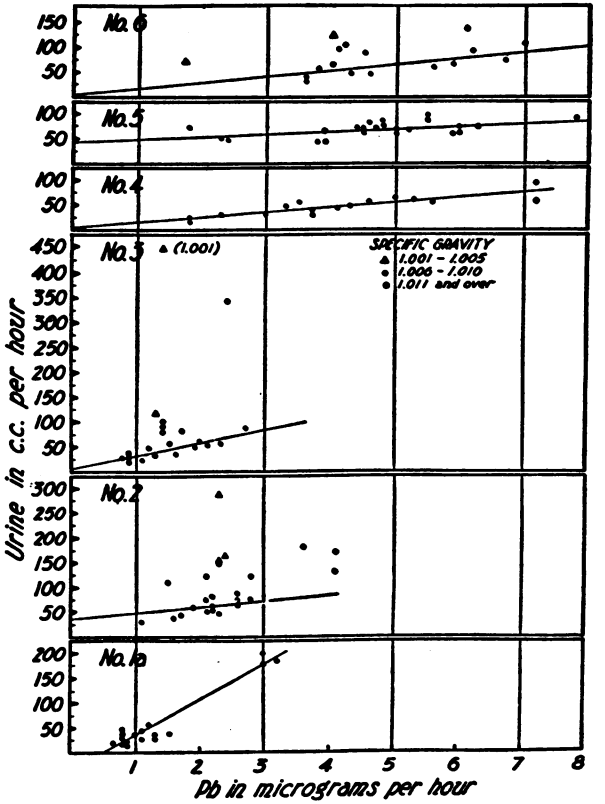

FIGURE 7.—Urinary lead rates and rates of urine excretion for 6 individuals. (Lines of regression were computed for specimens with a specific gravity in excess of 1.010.)

TOTAL URINARY OUTPUT

One of the facts disclosed by the computations was that in spite of wide variations in concentration and rate during the 3-day period, the total quantities of lead excreted from day to day by given individuals did not vary greatly in amount. This is shown in table 3 which gives the calculated 24-hour output of urinary lead as well as P_2O_5. The remarkable constancy of daily urinary lead output for given

individuals seems to be independent of excretion levels since it occurs in both consumers and orchardists alike.

For a given individual an increase in the amount of urinary phosphorus (calculated as P_2O_5) per sample was usually accompanied by an increase in the quantity of lead excreted (fig. 2).

These independent measurements have confirmed the phenomenon of diurnal variation of urinary lead excretion and suggest that the excretion of phosphorus and lead are chemically related. While the outputs of these two appear to be thus related, the ratio between total P_2O_5 and total Pb differs for different individuals. A given phosphate output is presumably dependent largely on the phosphate content of the diet and is therefore not associated with any fixed quantity of lead. Table 3 indicates that although the P_2O_5 output for both the consumers and orchardists fell into normal ranges, a given P_2O_5 output did not correspond to any fixed quantity of lead.

As might be expected no fixed relation was found between the quantity of lead in a specimen and the size of the single specimen for a given individual. The parallelism between the curves for total P_2O_5 output and total urine output was better and is shown especially in figure 6. In addition a few cases were noted (figs. 1A, 1B, and 6) in which an inverse relation was shown between lead concentrations and volume of water excreted.

TABLE 3.—*Total daily urinary output*

Class and subject No.	Lead (milligrams)				P_2O_5 (grams)		
	First day	Second day	Third day	Fourth day	First day	Second day	Third day
Personnel of Division of Industrial Hygiene:							
1A	0.026	0.026	0.026	----------	----------	----------	----------
1B	.020	.023	.020	0.017	----------	----------	----------
2	.060	.064	.048	----------	2.2	2.6	2.0
3	.032	.032	.032	----------	1.8	1.5	1.5
Orchardists:							
4	.088	.081	.052	----------	1.5	1.5	1.4
5	.11	.11	.10	----------	2.4	2.5	2.4
6	.12	.11	.12	----------	2.2	1.9	2.1

BLOOD LEAD MEASUREMENTS

Blood was drawn from two of the consumers (Nos. 2 and 3) on six occasions, using the technique for sampling and analysis previously described (*10*, *15*). While these samples were not numerous it was hoped that they might shed some light on the important relation between urinary and blood lead values. Table 4 indicates the values found, together with urine concentrations for specimens collected at nearly the same time.

TABLE 4.—*Comparison of blood and urinary lead concentration values for 2 subjects with no known exposure to lead arsenate*

Time	Subject No. 2		Subject No. 3	
	Urine (mg. per liter)	Blood (mg. per 100 g.)	Urine (mg. per liter)	Blood (mg. per 100 g.)
9:00 a. m.	0.023	0.081	0.046	0.045
12:30 p. m.	.015	.030	.040	.024
3:45 p. m.	.048	.033	.038	.031
9:00 a. m.	.032	.060	.014	.028
12:45 p. m.	.028	.055	.015	.031
3:45 p. m.	.040	.036	.017	.023

The random character of the blood values and lack of correspondence with the urine values is apparent. Moreover, no relation could be found between the blood values and other quantities. However, it will be noted that the initial blood values (ca. 9 a. m.) were always higher than the final values (at 3:45 p. m.). This is in agreement with Schmitt and Basse (*23*) who found that the first morning (fasting) blood specimens showed higher values than other samples taken throughout the day. Their observation that profound increase in water consumption with a corresponding diuretic effect caused a great temporary increase in blood lead values, together with the usually observed high initial values in the morning, may serve to explain the wide range of blood values frequently exhibited in given individuals within relatively short intervals of time.

While the blood lead measurements made in the present study are not extensive enough to establish the presence of diurnal variation, the results are in agreement with this view.

DIURNAL VARIATION OF URINARY ARSENIC EXCRETION

The amount of urine available after portions had been taken for lead and other determinations was frequently insufficient for arsenic analysis. However, the existence of diurnal variation in urinary arsenic excretion was found in three individuals [4] for whom specimens were available. One of the consumers with the most complete data showed a range in urinary arsenic excretion from 1.2 to 3.6 micrograms per hour with an average value of 2.0. The orchardist showed a range of 6.1 to 19.5 and an average of 11.4 micrograms per hour. The corresponding rates for urinary lead excretion were 2.6 and 5.1 micrograms per hour.

The data for these two individuals were not complete enough to enable the daily outputs of arsenic to be calculated. However, no relation was found between the arsenic and lead values. It is evident that the factors controlling the excretion of lead differ from those influencing the elimination of arsenic.

[4] Two consumers and one orchardist.

RELATION BETWEEN SINGLE URINE SAMPLES AND 24-HOUR SPECIMENS

It is evident from the foregoing discussion that diurnal variations of considerable magnitudes occur regularly both in those exposed and those not exposed to lead arsenate. Since neither concentrations, rates, nor outputs are constant from interval to interval it is difficult to determine an average value which will approximate that obtained with a 24-hour sample. The average of a number of samples collected during a day will approximate this result but will entail much more work for the analyses.

The first morning specimen appears to have considerable value in this connection. Table 6 gives a comparison of the lead concentrations of first morning specimens and the corresponding concentrations of calculated 24-hour samples.[5] It can be seen that the agreement between the averages for the 22 values was quite close, large deviations between the two kinds of measurements did not frequently occur, and the agreement was better for low lead levels than for higher ones.

TABLE 6.—*Comparison of urinary lead concentration values for first morning specimens and corresponding 24-hour specimens for two groups of persons*

Class and subject No.	Day	Pb concentration, first morning specimens	24-hour specimens (mg. per liter)	Difference
Consumers (personnel of Division of Industrial Hygiene):				
1A	First	0.022	0.027	0.005
	Second	.025	.031	.006
	Third	.018	.024	.006
1B	First	.010	.023	.013
	Second	.029	.017	.012
	Third	.020	.023	.003
	Fourth	.015	.014	.001
2	First	.037	.030	.007
	Second	.030	.023	.007
	Third	.035	.027	.008
3	First	.036	.038	.002
	Second	.029	.018	.011
	Third	.029	.021	.008
Average for class		.026	.024	.007
Orchardists (residents of Wenatchee, Wash.):				
4	First	.081	.089	.008
	Second	.084	.085	.001
	Third	.084	.087	.003
5	First	.101	.067	.034
	Second	.045	.067	.022
	Third	.053	.066	.013
6	First	.044	.053	.009
	Second	.043	.062	.019
	Third	.067	.087	.020
Average for class		.067	.074	.014

[5] The average concentration for the 24-hour period was obtained by adding together the amounts of lead in each sample collected during the 24 hours and dividing by the total 24-hour volume in liters.

The most important urinary lead measurement is the total amount excreted during a 24-hour period, since from this value can be calculated the corresponding concentration and the rate of excretion. The total amount may be obtained in one of two ways, either by analyzing the combined 24-hour output, or by analyzing all of the separate urine specimens excreted during this time. Except for research purposes, only the first method had practical value.

It is evident that comparisons of individual outputs may be useful in evaluating the degree of lead absorption. The amounts of lead excreted in the urine during 24-hour periods may therefore be compared for individuals or for groups of individuals.

The situation is quite different, however, for fractional day samples. It has been shown for six individuals that single specimens taken at random during the 24 hours may lead to widely differing analytical results. Comparison of individual concentration values thus obtained may have little significance since there is no fixed ratio of urinary lead concentration to total output. In the absence of 24-hour urine volumes, therefore, it is impossible to determine the total quantities excreted.

It has also been shown for the cases studied that by taking the first morning specimens the phenomenon of diurnal variation was minimized and in most cases the first morning specimens were representative samples of the corresponding 24-hour specimens. The concentration values thus obtained are therefore comparable for individual or group measurements. However, unless the 24-hour urine volumes have been measured the total lead outputs cannot be determined. Since the latter vary greatly, determination of the lead concentrations of urine samples from two individuals cannot be used to establish their 24-hour outputs.

In a subsequent study (*24*) the application of an average value for the 24-hour urine volume to concentration measurements for groups of individuals will be shown.

SUMMARY AND CONCLUSIONS

The occurrence of diurnal variation in urinary lead excretion has been demonstrated in the six cases studied. This phenomenon appears to take place independent of previous exposure of the individual or time of year.

A wide daily variation was shown for urinary lead concentration measurements as well as for the rate of lead excretion (in micrograms per hour) and for the total volume with all of the individuals studied. However, the total daily urinary lead outputs were remarkably constant for any one individual.

Relations were sought between various lead and phosphate measurements as well as with pH, specific gravity, and urine volume deter-

minations. A number of trends were found. An increase in the rate of urine excretion was generally paralleled by an increase in the rate of lead excretion for those specimens whose specific gravity was greater than 1.010. Marked diuresis was found not to increase greatly the rate of lead excretion nor the total quantity.

For a given individual an increase in the amount of urinary phosphorus (as P_2O_5) per sample was usually accompanied by an increase in the quantity of lead excreted. These independent measurements have confirmed the diurnal variation of urinary lead excretion and suggest that the excretion of lead and phosphorus are chemically related.

The determination of 12 blood lead values disclosed that the morning values were higher than the corresponding afternoon quantities. No relation between the blood lead values and other factors was apparent.

First morning specimens have been shown to be representative samples of the corresponding 24-hour specimens. The limitation of the fractional-day samples, that they give no measure of the total daily outputs, has been indicated.

Neither the urinary lead concentrations nor the rate of urinary lead excretion can be used as a measure of lead absorption when they are based on short-time measurements. The total 24-hour urinary lead output has more significance than any other measure of lead made on fractional-day samples.

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FREQUENCY OF DISABLING MORBIDITY BY CAUSE, AND DURATION, AMONG MALE AND FEMALE INDUSTRIAL WORKERS DURING 1940, AND BY CAUSE AMONG MALES DURING THE FIRST QUARTER OF 1941 [1]

By WILLIAM M. GAFAFER, *Senior Statistician, United States Public Health Service*

The quarterly reports for the year 1940 on the frequency of sickness and nonindustrial injuries causing disability for 8 consecutive calendar days or longer among a group of approximately 200,000 male members of 26 industrial sick benefit organizations have appeared (*1–4*). The present report records the experience among both males and females for the year 1940, and among males for the first quarter of 1941.

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

The last report of the series referring to the experience among females appeared in 1940 (*1*).

The year 1940.—Table 1 shows the experiences for males and females for 1940, with comparative data for earlier years. In a comparison of the frequencies for males during 1940 with the corresponding frequencies for 1935–39 the following differences are of interest: the 21 percent increase in bronchitis, the 38 percent increase in pneumonia, and the 22 percent increase in appendicitis.

A comparison of the frequencies for females for the same time periods shows over a 50 percent decrease for diseases of the stomach,

TABLE 1.—*Frequency of cases of sickness and nonindustrial injuries lasting 8 consecutive calendar days or longer among male and female employees in various industries, by cause, experience of 1940 and 1939, and the 5 years, 1935–39*

Cause (numbers in parentheses are disease title numbers from the International List of Causes of Death, 1939)	Annual number of cases per 1,000 persons					
	Males			Females		
	1940	1935–39 [1]	1939	1940	1935–39 [1]	1939
Sickness and nonindustrial injuries [2]	96.4	89.3	89.0	153.3	144.3	150.0
Percent of female rate	*63*	*62*	*59*			
Percent of male rate				*159*	*162*	*169*
Nonindustrial injuries (160–195)	11.8	11.2	10.3	14.0	13.0	13.0
Sickness [2]	84.6	78.1	78.7	139.3	131.3	137.0
Respiratory diseases	37.7	32.8	33.9	63.5	57.7	63.9
Influenza and grippe (33)	17.5	15.2	16.6	27.7	26.0	29.9
Bronchitis, acute and chronic (106)	5.2	4.3	4.1	8.2	7.3	7.3
Diseases of the pharynx and tonsils (part of 115)	4.9	4.8	4.4	12.7	12.3	11.6
Pneumonia, all forms (107–109)	3.6	2.6	3.0	1.8	1.5	2.0
Tuberculosis of the respiratory system (13)	.7	.8	.7	.6	.8	.9
Other respiratory diseases (104, 105, 110–114)	5.8	5.1	5.1	12.5	9.8	12.2
Nonrespiratory diseases	44.8	43.0	42.8	71.8	69.0	68.4
Digestive diseases	14.4	13.4	13.4	21.7	22.8	21.5
Diseases of the stomach, except cancer (117, 118)	3.9	3.8	3.5	1.2	2.6	2.2
Diarrhea and enteritis (120)	1.4	1.2	1.2	2.4	2.4	1.6
Appendicitis (121)	5.0	4.1	4.3	12.1	11.6	11.9
Hernia (part of 122)	1.5	1.6	1.5	.3	.5	.5
Other digestive diseases (part of 115 and 122, 116, 123–129)	2.6	2.7	2.9	5.7	5.7	5.3
Nondigestive diseases	30.4	29.6	29.4	50.1	46.2	46.9
Diseases of the heart (90–95)	2.9	2.5	2.9	2.7	1.5	1.8
Other circulatory diseases (96–103)	3.7	3.2	2.5	2.6	3.1	3.2
Nephritis, acute and chronic (130–132)	.4	.5	.4	.6	.4	.5
Other genitourinary diseases (133–139)	2.7	2.4	2.3	10.2	9.6	9.5
Neuralgia, neuritis, sciatica (part of 87)	2.3	2.2	2.2	2.6	2.1	2.1
Neurasthenia and the like (part of 84)	1.1	1.1	.9	5.4	5.9	5.7
Other diseases of the nervous system (80–83, 85, part of 84 and 87)	1.0	1.1	1.1	1.5	.8	1.2
Rheumatism, acute and chronic (58, 59)	4.0	3.9	3.5	3.1	3.1	2.4
Diseases of the organs of locomotion, except diseases of the joints (part of 156)	2.8	2.8	2.6	2.2	1.7	1.4
Diseases of the skin (151–153)	2.8	2.9	2.7	3.4	3.1	3.3
Infectious and parasitic diseases [3] (1–12, 14–24, 26–29, 31, 32, 34–44)	1.8	2.4	2.1	2.6	3.5	2.3
Cancer, all sites (45–55)	.6	.5	.6	.5	.5	.5
All other diseases (56, 57, 60–79, 88, 89, 140–150, 154, 155, 157, 162 (part of 156)	4.3	4.1	4.6	12.7	10.9	13.0
Ill-defined and unknown causes (200)	2.1	2.3	2.0	4.0	4.6	4.7
Number of person-years, all reporting organizations	216,621	896,606	188,595	16,318	77,697	15,343
Number of organizations	29		29	24		24

[1] Average of the 5 annual rates.
[2] Industrial injuries, venereal diseases, and a few numerically unimportant causes of disability are not reported.
[3] Except influenza, respiratory tuberculosis, and the venereal diseases.

except cancer, the 1940 rate being 1.2 cases per 1,000 while the rate for 1935–39 is 2.6. The average annual rate for this group of causes for the 9 years, 1932–40, is 2.8, the year 1940 yielding the lowest rate.

It will be observed that, while the total frequency for 1940, 1939, or 1935–39 is from 60 to 70 percent greater among the females than among the males, there are certain causes and cause groups that show for each of the 3 time periods lower rates among the females; these are pneumonia, diseases of the stomach except cancer, hernia, diseases of the heart, and rheumatism.[2]

TABLE 2.—*Frequency of ended cases of sickness and nonindustrial injuries disabling for the indicated number of consecutive calendar days, t, or more, male and female employees in various industries,[1] by broad cause group, cases beginning during the year 1940 and lasting at least 8 consecutive calendar days*

t days	Number of person-years of membership	Annual number of cases per 1,000 persons disabling for t days or more					
		Sickness and nonindustrial injuries	Respiratory diseases	Digestive diseases	Nonrespiratory nondigestive diseases	Ill-defined and unknown causes	Nonindustrial injuries
		Males					
8	85,566	103.5	40.5	16.8	33.5	1.3	11.4
15	85,566	65.1	18.6	13.8	24.1	1.0	7.6
22	85,566	47.5	10.9	11.9	18.4	.8	5.5
29	85,566	37.3	7.5	9.9	14.7	.6	4.6
36	85,566	30.0	5.7	8.0	12.1	.4	3.8
43	85,566	24.2	4.4	6.2	10.4	.3	2.9
50	85,566	19.7	3.4	4.8	8.9	.3	2.3
57	83,317	16.4	2.8	3.7	7.9	.2	1.8
64	82,740	13.9	2.2	2.9	7.2	.2	1.4
71	82,740	11.9	1.9	2.2	6.4	.2	1.2
78	72,539	10.8	1.9	1.9	5.9	.1	1.0
85	72,539	9.6	1.7	1.5	5.4	.1	.9
92	66,368	8.1	1.4	1.1	4.7	.1	.8
99	65,325	7.2	1.2	.8	4.4	.1	.7
190	45,055	1.8	.4	.1	1.3	----------	(3)
281	42,928	.7	.2	(3)	.5	----------	----------
372	42,928	.2	.1	----------	.1	----------	----------
Nonended cases	*85,566*	*1.9*	*.5*	*.1*	*1.1*	(3)	*.2*
Total, ended and nonended cases	*85,566*	*105.4*	*41.0*	*16.9*	*54.6*	*1.3*	*11.6*
		Females					
8	13,683	155.7	65.8	23.1	48.4	3.6	14.8
15	13,683	101.4	28.7	19.9	38.6	3.1	11.1
22	13,683	75.6	15.9	17.5	31.3	2.5	8.4
29	13,683	60.6	10.7	15.3	25.4	2.3	6.9
36	13,683	49.3	7.7	12.5	22.4	1.7	5.0
43	13,683	40.0	6.3	9.2	19.1	1.5	3.9
50	13,683	31.1	4.8	6.3	15.2	1.4	3.4
57	12,892	25.9	3.7	4.7	13.5	1.4	2.6
64	11,880	20.8	3.3	2.9	11.2	1.3	2.1
71	11,880	17.8	2.8	2.3	9.8	1.1	1.8
78	10,721	16.7	2.6	1.9	9.5	1.0	1.7
85	10,721	14.0	2.4	1.6	7.7	.9	1.4
92	9,731	11.9	2.2	1.4	6.5	.6	1.2
99	9,731	10.3	2.2	1.0	5.9	.3	.9
190	3,627	.8	----------	.3	.5	----------	----------
281	3,627	.6	----------	.3	.3	----------	----------
372	3,627	----------	----------	----------	----------	----------	----------
Nonended cases	*13,683*	*3.0*	*.4*	*.1*	*2.0*	*.3*	*.2*
Total, ended and nonended cases	*13,683*	*158.7*	*66.3*	*23.2*	*60.3*	*3.9*	*15.0*

[1] "Various industries" includes all of the reporting industries that submitted data on individual case durations. The males are represented by 26 industries, the females by 21.
[2] Less than 0.05 case per 1,000.

[2] Summation or neuralgia, neuritis, and sciatica; rheumatism, acute and chronic; and diseases of the organs of locomotion except diseases of the joints.

Case duration.—Table 2 shows the frequency of ended cases lasting a certain number of days, *t*, or longer, by sex and broad cause group. Thus, among the males the frequency of ended cases accounted for by all causes and lasting 15 days or longer is 65.1 per 1,000 while the corresponding frequency for the females is 101.4. The magnitude of the rapidity of decrease of the frequencies with increasing values of *t* is determined by whether or not there is a preponderance of long or short cases, the long cases inhibiting the rate of decrease while the short ones accelerate it. Thus, while the group of respiratory diseases, when compared with the other cause groups, shows the highest initial frequency for both males and females, the decrease of the frequencies of this group is rapid because of the relatively large number of short cases.[3]

TABLE 3.—*Frequency of cases of sickness and nonindustrial injuries lasting 8 consecutive calendar days or longer among MALE employees in various industries by cause, the first quarter of 1941 compared with the first quarters of 1940 and 1939* [1]

Cause (numbers in parentheses are disease title numbers from the International List of Causes of Death, 1939)	Annual number of cases per 1,000 males for the first quarter		
	1941	1940	1939
Sickness and nonindustrial injuries [2]	138.2	134.8	125.3
Nonindustrial injuries (169–195)	11.3	12.6	9.6
Sickness [2]	126.9	122.2	115.7
Respiratory diseases	78.9	69.9	65.9
Influenza and grippe (33)	50.7	39.4	39.9
Bronchitis, acute and chronic (106)	7.8	8.7	6.6
Diseases of the pharynx and tonsils (part of 115)	5.5	6.1	5.7
Pneumonia, all forms (107–109)	5.8	6.2	4.7
Tuberculosis of the respiratory system (13)	.5	.7	.8
Other respiratory diseases (104, 105, 110–114)	8.6	8.8	8.2
Nonrespiratory diseases	44.9	50.1	47.4
Digestive diseases	14.4	15.4	14.2
Diseases of the stomach, except cancer (117, 118)	3.8	4.1	3.6
Diarrhea and enteritis (120)	1.2	1.4	1.1
Appendicitis (121)	5.1	5.5	4.5
Hernia (part of 122)	1.6	1.4	1.4
Other digestive diseases (part of 115 and 122, 116, 123–129)	2.7	3.0	3.6
Nondigestive diseases	30.5	34.7	33.2
Diseases of the heart and arteries, and nephritis (90–99, 102, 130–132)	4.5	5.2	5.3
Other genitourinary diseases (133–138)	2.1	3.0	2.3
Neuralgia, neuritis, sciatica (part of 87)	3.1	2.9	2.3
Neurasthenia and the like (part of 84)	.8	1.1	1.0
Other diseases of the nervous system (80–83, 85, part of 84 and 87)	1.1	1.2	1.1
Rheumatism, acute and chronic (58, 59)	4.7	4.6	4.5
Diseases of the organs of locomotion, except diseases of the joints (part of 156)	2.9	3.4	3.1
Diseases of the skin (151–153)	2.3	3.2	2.7
Infectious and parasitic diseases [3] (1–12, 14–24, 26–29, 31, 32, 34–44)	2.4	2.2	3.0
All other diseases (45–57, 60–79, 88, 89, 100, 101, 103, 154, 155, 157, 162, part of 156)	7.6	7.9	7.9
Ill-defined and unknown causes (200)	3.1	2.2	2.4
Average number of males covered in the record	223,684	196,766	170,649
Number of organizations	26	26	26

[1] The same 26 organizations are included in 1941, 1940, and 1939.
[2] Industrial injuries, venereal diseases, and a few numerically unimportant causes of disability are not reported.
[3] Except influenza, respiratory tuberculosis, and the venereal diseases.

[3] Item 5 in the list of references contains further details on the behavior of frequency in relation to duration.

First quarter of the year 1941.—The morbidity experience among the male members of 26 industrial sick benefit organizations for the first quarter of 1941 as compared with the corresponding quarter of 1940 and 1939 is shown in table 3. Interest in the table centers around the frequency for influenza and grippe with its increase of approximately 30 percent when compared with 1940 or 1939. The rate for the first quarter of 1941 (50.7) is sufficiently large to indicate an epidemic. During the 13-year period, 1929–41, this rate was equalled in 1931 and exceeded in 1929 (77.4) and 1937 (60.9), the mean for the 13 first quarter rates being 39.3.

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DEATHS DURING WEEK ENDED AUGUST 30, 1941

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

	Week ended Aug. 30, 1941	Corresponding week, 1940
Data from 87 large cities of the United States:		
Total deaths	7,091	7,274
Average for 3 prior years	7,125	
Total deaths, first 35 weeks of year	299,165	300,015
Deaths per 1,000 population, first 35 weeks of year, annual rate	11.9	12.0
Deaths under 1 year of age	535	498
Average for 3 prior years	489	
Deaths under 1 year of age, first 35 weeks of year	18,380	17,600
Data from industrial insurance companies:		
Policies in force	64,441,524	64,944,214
Number of death claims	9,397	10,089
Death claims per 1,000 policies in force, annual rate	7.6	8.1
Death claims per 1,000 policies, first 35 weeks of year, annual rate	9.7	9.9

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 6, 1941

Summary

The number of cases of poliomyelitis reported during the current week dropped to 584 as compared with 624 for the preceding week. While the rate of increase declined during each of the preceding two weeks, this is the first week since June 14 in which a decrease has been recorded for the total number of cases reported.

The following listed 13 States reported 15 or more cases during the current week (last week's figures in parentheses): New York, 71 (69); Pennsylvania 66 (65); Alabama 66 (65); Georgia 49 (50); Tennessee 38 (29); Ohio 33 (36); New Jersey 32 (29); Minnesota 23 (21); Illinois 21 (31); Massachusetts 18 (21); Kentucky 18 (15); Maryland 16 (32); Virginia 15 (5) These are the same States which reported 15 or more cases last week, with the exception that Virginia is included currently while the numbers of cases in Michigan and Florida dropped below 15.

A total of 4,609 cases of poliomyelitis has been reported in the United States this year to date (first 36 weeks), as compared with 5,512 for the corresponding period in 1937, when the largest number of cases was reported for this period during the preceding 5 years (1936–40), and with 4,059 in 1940, the next highest year.

The number of cases of encephalitis increased in North Dakota from 98 to 151, while the incidence decreased in Minnesota from 51 to 30, in South Dakota from 13 to 11, and in Colorado from 32 to 24. From August 16 to 30, 24 cases were reported in Wisconsin, distributed throughout the State.[1]

All of the 12 cases of Rocky Mountain spotted fever reported during the current week, with the exception of 1 case in Missouri, occurred in States east of the Mississippi River. Of 86 cases of endemic typhus fever, 39 cases occurred in Georgia and 15 in Texas. One case was reported in New York City.

The death rate for the current week in 88 large cities in the United States was 10.4 per 1,000 population, as compared with 9.9 for the preceding week and the 3-year (1938–40) average. The accumulative rate to date (first 36 weeks) is 11.9, which is the same as for the corresponding period in 1940.

[1] For recent reports of encephalitis in the Province of Manitoba, Canada, see p. 1861.

Telegraphic morbidity reports from State health officers for the week ended September 6, 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. 6, 1941	Sept. 7, 1940		Sept. 6, 1941	Sept. 7, 1940		Sept. 6, 1941	Sept. 7, 1940		Sept. 6, 1941	Sept. 7, 1940	
NEW ENG.												
Maine	0	1	1	-------	-------	-------	12	14	1	0	0	0
New Hampshire	0	0	0	-------	-------	-------	1	0	0	0	0	0
Vermont	1	0	0	-------	-------	-------	25	0	2	1	0	0
Massachusetts	0	2	2	-------	-------	-------	34	31	21	1	0	1
Rhode Island	0	0	0	-------	-------	-------	1	0	-------	1	0	0
Connecticut	0	0	0	-------	1	1	10	5	5	0	0	0
MID. ATL.												
New York [1]	4	8	13	[3]1	[3]8	[3]2	71	102	74	7	2	3
New Jersey	2	4	3	2	5	5	33	43	13	0	0	1
Pennsylvania	10	5	10	-------	-------	-------	76	33	33	4	4	2
E. NO. CEN.												
Ohio [3]	10	3	14	7	19	2	18	18	12	2	1	1
Indiana	4	4	7	19	8	8	2	5	6	0	1	1
Illinois [3]	16	9	11	-------	3	3	84	23	21	2	0	1
Michigan [4]	3	4	5	-------	5	-------	11	51	13	0	1	1
Wisconsin	0	1	2	13	15	15	61	53	28	1	1	1
W. NO. CEN.												
Minnesota	6	7	5	-------	1	1	4	9	9	0	0	0
Iowa	2	4	4	-------	4	-------	3	8	3	1	0	0
Missouri [3]	4	8	12	11	1	5	6	2	2	1	0	0
North Dakota	1	6	1	7	2	-------	6	0	0	0	0	0
South Dakota	9	1	0	-------	-------	-------	2	0	0	0	0	0
Nebraska	0	1	1	-------	-------	-------	1	2	1	0	1	0
Kansas	0	4	7	2	1	1	1	4	3	1	1	0
SO. ATL.												
Delaware	0	1	0	-------	-------	-------	1	1	-------	0	0	0
Maryland [3 4]	0	1	3	-------	2	2	20	5	4	2	0	0
Dist. of Col	1	1	1	-------	-------	1	6	1	1	0	0	0
Virginia [3]	12	8	37	119	76	-------	34	10	8	4	0	2
West Virginia [3 4]	5	7	7	-------	15	10	21	2	1	2	3	1
North Carolina [1 3]	34	24	38	-------	1	1	24	8	8	1	3	2
South Carolina [1]	41	7	24	93	120	120	27	18	5	0	0	0
Georgia [1]	23	10	31	19	14	-------	39	2	-------	1	0	1
Florida [1]	8	3	8	2	1	-------	4	2	2	0	0	1
E. SO. CEN.												
Kentucky	11	3	12	-------	1	5	6	7	7	3	0	2
Tennessee [1]	25	8	17	2	11	11	25	25	7	4	0	1
Alabama [1]	33	6	31	2	3	6	2	5	3	1	1	1
Mississippi [4]	10	18	19	-------	-------	-------	-------	-------	-------	1	2	0
W. SO. CEN.												
Arkansas	15	5	9	4	3	3	21	8	4	0	0	0
Louisiana [1]	4	7	5	1	-------	3	3	2	2	0	0	0
Oklahoma	8	3	8	20	15	15	6	2	4	0	0	0
Texas [1 4]	27	13	28	329	101	58	48	15	15	1	1	2
MOUNTAIN												
Montana	3	0	1	-------	4	4	2	4	2	0	0	0
Idaho	0	0	1	-------	-------	-------	0	0	1	0	0	0
Wyoming	0	0	0	8	-------	-------	3	1	1	0	0	0
Colorado	8	13	5	36	1	-------	13	3	9	1	0	1
New Mexico	0	5	5	-------	-------	-------	5	5	3	0	0	0
Arizona	1	0	0	25	10	14	23	3	3	1	0	0
Utah [4]	0	1	0	3	2	1	9	6	3	0	0	0
Nevada	0	-------	-------	-------	-------	-------	1	-------	-------	0	-------	-------
PACIFIC												
Washington	0	0	1	-------	-------	-------	3	8	8	1	2	1
Oregon	1	3	1	3	1	4	7	5	4	1	0	0
California	7	8	13	18	4	11	62	25	23	0	0	1
Total	349	227	453	746	458	458	877	576	495	46	24	36
36 weeks	8,424	9,458	14,870	601,643	170,447	152,791	833,081	230,613	271,308	1,513	1,235	2,250

See footnotes at end of table.

Telegraphic morbidity reports from State health officers for the week ended September 6, 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. 6, 1941	Sept. 7, 1940		Sept. 6, 1941	Sept. 7, 1940		Sept. 6, 1941	Sept. 7, 1940		Sept. 6, 1941	Sept. 7, 1940	
NEW ENG.												
Maine	2	0	1	7	0	1	0	0	0	1	1	1
New Hampshire	1	0	0	2	1	0	0	0	0	0	0	0
Vermont	0	0	0	2	0	1	0	0	0	2	0	0
Massachusetts	18	3	3	31	22	22	0	0	0	2	2	3
Rhode Island	0	0	0	2	1	2	0	0	0	0	3	1
Connecticut	6	2	3	8	4	7	0	0	0	0	4	3
MID. ATL.												
New York [1]	71	17	20	66	56	56	0	0	0	17	11	20
New Jersey	32	4	4	28	26	18	0	0	0	3	3	7
Pennsylvania	66	11	11	35	52	52	0	0	0	22	30	30
E. NO. CEN.												
Ohio [2]	33	56	17	48	52	52	0	0	0	22	26	26
Indiana	4	81	3	9	16	17	0	0	1	7	9	9
Illinois [3]	21	40	30	40	75	78	1	0	0	10	17	35
Michigan [4]	7	139	49	18	47	59	0	0	0	6	7	10
Wisconsin	6	30	5	37	48	46	1	0	0	2	0	3
W. NO. CEN.												
Minnesota	23	12	12	18	20	20	0	0	0	0	1	2
Iowa	1	80	3	16	13	16	0	0	1	3	0	2
Missouri [3]	1	32	2	19	13	13	0	0	0	11	9	23
North Dakota	4	0	0	2	2	5	0	0	0	2	0	2
South Dakota	1	9	2	4	3	3	0	0	0	0	0	0
Nebraska	0	18	1	2	2	3	0	0	0	0	0	0
Kansas	6	58	0	30	24	31	0	0	0	1	7	7
SO. ATL.												
Delaware	0	0	0	2	1	0	0	0	0	2	2	1
Maryland [3 4]	16	0	1	11	13	14	0	0	0	5	1	9
Dist. of Col.	7	0	0	3	2	3	0	0	0	1	0	0
Virginia [3]	15	17	4	8	16	17	0	0	0	16	12	15
West Virginia [3 4]	2	51	2	8	15	19	0	0	0	9	9	19
North Carolina [1 3]	12	5	1	26	38	34	0	0	0	3	16	13
South Carolina [1]	10	1	1	11	7	7	0	0	0	17	21	19
Georgia [1]	49	0	0	16	19	14	0	0	0	15	39	24
Florida [1]	4	0	1	6	1	4	0	0	0	1	2	2
E. SO. CEN.												
Kentucky	18	17	4	23	20	27	0	0	0	32	13	38
Tennessee [1]	38	3	3	25	0	25	0	0	0	30	24	27
Alabama [1]	66	2	4	16	13	13	0	0	0	11	12	12
Mississippi [4]	10	1	1	7	9	9	0	0	0	10	13	13
W. SO. CEN.												
Arkansas	1	3	1	4	3	8	0	0	0	12	36	24
Louisiana [1]	3	2	2	4	2	3	0	0	0	15	25	19
Oklahoma	1	6	2	11	9	8	0	0	0	12	28	28
Texas [1 4]	3	4	4	18	11	24	0	0	0	26	50	47
MOUNTAIN												
Montana	1	8	1	1	11	5	0	0	1	1	1	2
Idaho	0	2	0	2	10	2	0	0	0	0	2	3
Wyoming	2	0	0	1	2	2	0	0	1	1	0	0
Colorado	3	3	3	15	11	8	0	0	2	3	6	6
New Mexico	1	1	1	1	0	5	0	0	0	2	9	8
Arizona	0	0	0	2	1	1	0	0	0	3	3	3
Utah [4]	4	0	0	0	4	4	0	0	0	0	0	1
Nevada	0	----	----	0	----	----	0	----	----	0	----	----
PACIFIC												
Washington	2	14	2	11	5	10	0	0	8	2	1	2
Oregon	6	5	4	7	3	6	0	0	2	3	1	3
California	7	21	25	26	45	51	0	0	2	4	7	15
Total	554	758	436	689	748	910	2	0	28	347	463	606
36 weeks	4,609	4,059	3,445	93,759	120,804	139,717	1,197	1,988	8,136	5,499	6,247	8,743

See footnotes at end of table.

Telegraphic morbidity reports from State health officers for the week ended September 6, 1941, and comparison with corresponding week of 1940—Con.

Division and State	Whooping cough	
	Week ended	
	Sept. 6, 1941	Sept. 7, 1940
NEW ENG.		
Maine	13	38
New Hampshire	1	0
Vermont	6	11
Massachusetts	81	72
Rhode Island	25	0
Connecticut	26	44
MID. ATL.		
New York [1]	270	266
New Jersey	116	95
Pennsylvania	185	250
E. NO. CEN.		
Ohio [2]	322	335
Indiana	26	11
Illinois [2]	231	176
Michigan [4]	190	173
Wisconsin	232	73
W. NO. CEN.		
Minnesota	75	22
Iowa	26	25
Missouri [3]	64	30
North Dakota	22	3
South Dakota	9	2
Nebraska	2	8
Kansas	81	33
SO. ATL.		
Delaware	0	7
Maryland [3 4]	47	61
Dist. of Col	19	3
Virginia [3]	71	80
West Virginia [3 4]	16	38
North Carolina [1 3]	109	60
South Carolina [1]	84	16
Georgia [1]	20	23
Florida [1]	9	0
E. SO. CEN.		
Kentucky	74	41
Tennessee [1]	59	33
Alabama [1]	14	7
Mississippi [4]	----------	----------
W. SO. CEN.		
Arkansas	13	19
Louisiana [1]	0	4
Oklahoma	8	12
Texas [1 4]	149	134
MOUNTAIN		
Montana	6	8
Idaho	0	0
Wyoming	19	3
Colorado	85	14
New Mexico	1	18
Arizona	7	2
Utah [4]	25	24
Nevada	0	----------
PACIFIC		
Washington	48	48
Oregon	20	5
California	191	215
Total	3,097	2,542
36 weeks	155,948	114,846

[1] Typhus fever, week ended Sept. 6, 1941, 86 cases as follows: New York, 1; North Carolina, 1; South Carolina, 2; Georgia, 39; Florida, 11; Tennessee, 1; Alabama, 8; Louisiana, 8; Texas, 15.

[2] New York City only.

[3] Rocky Mountain spotted fever, week ended Sept. 6, 1941, 12 cases as follows: Ohio, 2; Illinois, 1; Missouri, 1; Maryland, 1; Virginia, 2; West Virginia, 2; North Carolina, 3.

[4] Period ended earlier than Saturday.

WEEKLY REPORTS FROM CITIES

City reports for week ended August 23, 1941

This table lists the reports from 131 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	0	0	2	19
New Hampshire:											
Concord	0	------	0	0	0	0	0	0	0	0	15
Manchester	0	------	0	0	0	0	0	0	0	0	15
Nashua	0	------	0	0	0	0	0	1	0	8	5
Vermont:											
Burlington	0	------	0	0	0	0	0	0	0	0	8
Rutland	0	------	0	0	0	0	0	0	0	0	5
Massachusetts:											
Boston	0	------	0	10	5	19	0	2	1	18	140
Fall River	4	------	0	0	1	3	0	1	0	0	20
Springfield	0	------	0	7	0	1	0	0	0	5	25
Worcester	0	------	0	1	0	0	0	1	0	9	34
Rhode Island:											
Pawtucket	2	------	0	0	0	0	0	0	0	0	15
Providence	1	------	0	0	1	3	0	0	0	14	39
Connecticut:											
Bridgeport	0	------	0	0	1	1	0	1	1	1	25
Hartford	0	------	0	0	4	0	0	1	0	0	43
New Haven	0	------	0	5	0	0	0	0	1	5	38
New York:											
Buffalo	0	------	0	0	4	4	0	4	0	18	119
New York	7	------	0	16	30	18	0	75	9	130	1,158
Rochester	0	------	0	3	2	1	0	3	0	2	71
Syracuse	0	------	0	1	0	1	0	0	0	22	38
New Jersey:											
Camden	1	------	0	0	2	0	0	2	0	1	27
Newark	0	------	1	2	3	3	0	2	0	26	68
Trenton	0	------	0	0	1	3	0	1	2	0	21
Pennsylvania:											
Philadelphia	2	------	1	1	8	6	0	15	1	67	330
Pittsburgh	1	------	0	1	10	4	0	9	-------	34	127
Reading	0	------	0	0	1	0	0	0	0	2	17
Scranton	0	------	--------	1	-------	0	0	-------	0	2	--------
Ohio:											
Cincinnati	0	------	1	0	0	2	0	4	0	9	112
Cleveland	0	1	0	0	2	4	0	5	0	80	148
Columbus	0	------	0	3	0	2	0	3	0	8	84
Toledo	0	------	0	4	3	0	0	4	1	41	64
Indiana:											
Anderson	0	------	0	0	0	0	0	0	0	0	7
Fort Wayne	0	------	0	0	2	0	0	0	0	0	18
Indianapolis	0	------	0	1	3	1	0	3	0	5	69
Muncie	0	------	0	0	1	2	0	0	0	0	9
South Bend	0	------	0	0	0	0	0	0	0	0	11
Terre Haute	0	------	0	0	1	0	0	0	0	0	18
Illinois:											
Alton	0	------	0	0	0	0	0	0	0	0	9
Chicago	4	1	0	4	9	15	0	44	1	142	578
Elgin	0	------	0	1	1	2	0	0	0	1	9
Moline	0	------	0	0	0	0	0	0	0	3	13
Springfield	0	------	0	0	1	1	0	0	0	1	18
Michigan:											
Detroit	3	------	0	2	8	7	0	11	3	71	227
Flint	0	------	0	1	0	1	0	0	0	0	22
Grand Rapids	0	------	0	1	0	0	0	0	1	12	38
Wisconsin:											
Kenosha	0	------	0	1	0	0	0	0	0	0	6
Madison	0	------	0	0	0	0	0	0	0	3	12
Milwaukee	0	------	0	12	3	3	0	4	0	135	107
Racine	0	------	0	1	0	1	0	0	0	4	15
Superior	0	------	0	0	0	0	0	0	0	9	7
Minnesota:											
Duluth	0	------	0	0	1	1	0	0	0	8	20
Minneapolis	0	------	1	1	1	2	0	1	0	9	100
St. Paul	0	------	0	1	1	1	0	0	0	25	43
Iowa:											
Cedar Rapids	0	------	--------	0	-------	0	0	-------	0	1	--------
Des Moines	0	------	--------	0	-------	2	0	-------	1	0	27
Sioux City	0	------	--------	0	-------	0	0	-------	0	14	--------
Waterloo	0	------	--------	0	-------	0	0	-------	0	2	--------

City reports for week ended August 23, 1941—Continued

State and city	Diphtheria cases	Influenza cases	Influenza deaths	Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases	Deaths, all causes
Missouri:											
Kansas City	1	------	0	1	2	4	0	2	1	3	72
St. Joseph	0	------	0	0	5	0	0	0	0	1	22
St. Louis	2	1	0	3	6	6	0	5	2	22	177
North Dakota:											
Fargo	0	------	0	0	0	0	0	0	0	0	9
Grand Forks	0	------	--------	0	-------	0	0	--------	0	2	--------
Minot	0	------	--------	3	-------	0	0	-------	0	1	3
South Dakota:											
Aberdeen	0	------	--------	0	-------	0	0	-------	0	1	--------
Sioux Falls	1	------	--------	0	-------	0	0	-------	0	0	9
Nebraska:											
Lincoln	0	------	--------	1	-------	0	0	-------	0	0	--------
Omaha	0	------	0	0	2	0	0	1	0	0	49
Kansas:											
Lawrence	0	------	0	0	0	0	0	0	0	0	8
Topeka	0	------	0	0	4	1	0	0	0	11	14
Wichita	0	------	0	0	3	1	0	0	0	1	21
Delaware:											
Wilmington	0	------	0	0	1	1	0	0	0	0	23
Maryland:											
Baltimore	1	2	0	24	6	0	0	8	1	27	178
Cumberland	0	------	0	0	0	1	0	0	0	0	12
Frederick	0	------	0	0	0	0	0	0	0	0	4
Dist. of Col.:											
Washington	0	------	0	7	2	4	0	8	2	23	138
Virginia:											
Lynchburg	1	------	0	2	0	0	0	1	1	0	12
Norfolk	0	------	0	0	1	1	0	1	0	0	24
Richmond	0	------	1	1	1	3	0	1	1	0	42
Roanoke	0	------	0	0	0	0	0	0	0	2	21
West Virginia:											
Charleston	0	------	0	0	0	0	0	0	0	1	12
Huntington	0	------	--------	0	-------	1	0	--------	0	0	--------
Wheeling	0	------	0	2	2	0	0	0	0	0	18
North Carolina:											
Gastonia	0	------	--------	0	-------	2	0	--------	0	0	--------
Wilmington	0	------	0	1	0	0	0	1	0	6	8
Winston-Salem	1	------	0	2	3	0	0	3	0	0	24
South Carolina:											
Charleston	0	1	0	0	0	1	0	0	1	3	20
Greenville	0	------	0	0	0	0	0	0	0	2	4
Georgia:											
Atlanta	1	2	0	12	1	1	0	6	1	2	75
Brunswick	0	------	0	0	0	0	0	0	0	0	2
Savannah	0	1	0	1	0	2	0	1	2	0	19
Florida:											
Miami	0	------	0	0	1	0	0	0	1	16	35
St. Petersburg	0	------	0	0	1	0	0	0	0	0	16
Tampa	0	1	0	0	0	0	0	0	1	0	22
Kentucky:											
Ashland	0	------	0	0	0	0	0	0	1	1	9
Covington	0	------	0	0	1	0	0	3	0	0	15
Lexington	0	------	0	0	0	0	0	0	0	5	12
Louisville	1	------	0	2	0	4	0	4	0	12	43
Tennessee:											
Knoxville	0	------	0	1	0	2	0	0	1	4	28
Memphis	0	------	0	1	0	1	0	3	2	15	78
Nashville	0	------	0	0	1	0	0	1	0	8	47
Alabama:											
Birmingham	1	------	0	1	3	1	0	2	1	3	75
Mobile	0	------	0	0	1	0	0	1	0	0	23
Montgomery	0	------	--------	0	-------	0	0	-------	0	0	--------
Arkansas:											
Fort Smith	0	------	--------	0	-------	0	0	-------	0	0	--------
Little Rock	1	1	0	4	2	0	0	1	0	0	34
Louisiana:											
Lake Charles	0	------	0	0	1	0	0	0	0	0	8
New Orleans	2	------	0	0	10	0	0	15	0	12	163
Shreveport	0	------	0	0	2	0	0	1	0	0	17
Oklahoma:											
Oklahoma City	0	------	0	0	2	0	0	0	0	0	36
Tulsa	0	------	0	0	3	3	0	0	0	1	12
Texas:											
Dallas	4	------	0	6	0	2	0	0	0	1	59
Fort Worth	0	------	0	0	0	0	0	0	1	6	44
Galveston	0	------	0	0	3	0	0	0	0	2	20
Houston	0	------	0	1	3	4	0	6	2	17	78
San Antonio	0	1	1	0	4	0	0	9	0	1	82
Montana:											
Billings	0	------	0	0	0	1	0	0	0	4	4
Helena	0	------	0	0	0	0	0	0	0	0	5
Missoula	0	------	0	0	1	0	0	0	0	0	4

City reports for week ended August 23, 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								
Idaho:											
Boise	0	------	0	0	0	0	0	0	0	0	5
Colorado:											
Denver	7	12	0	10	4	3	0	4	0	73	77
Pueblo	0	------	0	0	1	2	0	0	0	4	7
New Mexico:											
Albuquerque	0	------	0	0	0	0	0	2	0	0	19
Arizona:											
Phoenix	0	5	--------	1	-------	0	0	-------	0	7	--------
Utah:											
Salt Lake City	0	------	0	0	0	1	0	0	1	16	28
Washington:											
Seattle	0	------	0	0	0	2	0	1	0	11	95
Spokane	0	------	0	0	0	3	0	1	3	5	36
Tacoma	0	------	0	0	2	0	0	0	0	6	33
Oregon:											
Portland	0	------	0	2	1	0	0	1	0	0	70
Salem	0	------	--------	0	-------	0	0	-------	1	0	--------
California:											
Los Angeles	0	6	1	9	3	8	0	15	0	25	313
Sacramento	0	------	0	0	1	1	0	1	0	3	26
San Francisco	0	------	0	3	2	3	0	5	0	13	162

State and city	Meningitis, meningococcus		Poliomyelitis cases	State and city	Meningitis, meningococcus		Poliomyelitis cases
	Cases	Deaths			Cases	Deaths	
Maine:				Maryland:			
Portland	0	0	1	Baltimore	1	0	13
Massachusetts:				Cumberland	0	0	1
Boston	0	0	2	Frederick	0	0	1
Worcester	0	0	1	District of Columbia:			
Rhode Island:				Washington	0	0	6
Providence	0	0	2	Virginia:			
Connecticut:				Norfolk	0	0	1
Hartford	0	0	1	South Carolina:			
New Haven	0	0	1	Greenville	0	0	1
New York:				Charleston	0	0	1
Buffalo	0	0	3	Georgia:			
New York	2	0	32	Atlanta	0	0	4
Rochester	0	0	1	Florida:			
New Jersey:				Miami	0	0	1
Camden	0	0	1	Kentucky:			
Newark	0	0	1	Louisville	0	0	2
Pennsylvania:				Tennessee:			
Philadelphia	0	0	14	Knoxville	0	0	2
Pittsburgh	0	0	2	Nashville	0	0	4
Ohio:				Alabama:			
Cincinnati	0	0	2	Birmingham	0	0	8
Cleveland	1	0	27	Montgomery	0	0	3
Toledo	0	0	1	Louisiana:			
Indiana:				New Orleans	0	0	1
South Bend	0	0	1	Shreveport	0	1	0
Terre Haute	1	1	0	Oklahoma:			
Illinois:				Tulsa	0	0	1
Chicago	1	2	11	Texas:			
Michigan:				Houston	0	0	3
Detroit	1	0	7	Utah:			
Wisconsin:				Salt Lake City	0	0	1
Madison	0	0	3	Oregon:			
Minnesota:				Portland	0	0	1
Duluth	0	0	1	Salem	0	0	1
Minneapolis	0	0	1	California:			
St. Paul	0	0	6	Los Angeles	0	0	4
Missouri:				San Francisco	1	0	0
St. Louis	0	0	3				
Delaware:							
Wilmington	0	0	2				

Encephalitis, epidemic or lethargic.—Cases: New York, 4; Madison, 2; Minneapolis, 14; St. Paul, 4; Sioux City, 2; Fargo, 9; Grand Forks, 6 (also 11 old cases not reported before in Grand Forks); Minot, 21; Aberdeen, 2; Baltimore, 1; Denver, 4. Deaths: New York, 1; Madison, 1; Minneapolis, 4; St. Paul, 1; Fargo, 4; Aberdeen, 1; Topeka, 1; Baltimore, 1.

Pellagra.—Cases: Boston, 1.

Typhus fever.—Cases: New York, 2; Charleston, S. C., 1; Atlanta, 4; Brunswick, 2; Savannah, 4; Miami, 1; Birmingham, 1; Mobile, 1; Montgomery, 1; Lake Charles, 1; New Orleans, 4; Houston, 2. Deaths: Savannah, 1; Fort Worth, 1.

Rates (annual basis) per 100,000 population for a group of 87 selected cities (population, 1940, 33,841,378)

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 Aug. 23, 1941	6.9	4.6	1.1	25.6	28.8	25.4	0.0	45.5	6.5	134.1
Average, 1936–40	10.7	4.2	1.6	31.5	39.1	33.5	0.8	51.1	11.1	180.4

PLAGUE INFECTION IN FLEAS IN KERN AND SISKIYOU COUNTIES, CALIF.

Under date of August 26, 1941, Dr. Bertram P. Brown, Director of Public Health of California, reported plague infection proved, by animal inoculation and cultures, in a pool of 207 fleas from 19 ground squirrels, *C. beecheyi*, submitted to the laboratory on July 14 from a ranch at Keene, Kern County, Calif.

Under the same date Dr. Brown also reported plague infection proved, by animal inoculation and cultures, in 3 pools of fleas from ground squirrels, *C. douglasii*, in Siskiyou County, Calif., as follows: One a pool of 136 fleas from 4 ground squirrels submitted to the laboratory on July 23 from a ranch 2 miles east and one-half mile south of Yreka, another a pool of 43 fleas from 2 ground squirrels submitted to the laboratory on August 8 from a location 1 mile north and 2 miles west of Weed, and the third a pool of 50 fleas from 7 ground squirrels taken on August 8 from a ranch 1½ miles north and 2½ miles west of Weed.

FOREIGN REPORTS

CANADA

Provinces—Communicable diseases—Week ended August 2, 1941.—During the week ended August 2, 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	4	7	2			4	18
Chickenpox		6		23	70	9	22	17	24	171
Diphtheria	4	9	2	14		1				30
Dysentery				2						2
Influenza					4		7		5	16
Lethargic encephalitis						2				2
Measles		9		262	100	8	16	6	64	465
Mumps				40	51	5	15	12		123
Pneumonia		3			2		1		5	11
Poliomyelitis			24	3		78	4	1	2	112
Scarlet fever		7	2	43	56	2		6	5	121
Trachoma									1	1
Tuberculosis	1	12	17	101	22	2		4		159
Typhoid and paratyphoid fever			3	26	4		1		1	35
Whooping cough			3	41	191	2	7	2	11	257

Manitoba—Poliomyelitis.—During the week ended September 5, 1941, 78 new cases of poliomyelitis were reported in Manitoba, making a total of 758 cases since June 30, 1941.

Encephalitis.—During the week ended September 5, 1941, 70 cases of encephalitis have been reported bringing the total number to 409 in Manitoba since August 1, 1941.

According to recent information, a report made by the Rockefeller Institute of Medical Research stated that the first blood sample from a patient in Winnipeg during the present epidemic indicated that the disease was caused by the western equine type of virus.

The record of encephalitis in Winnipeg since 1919 indicates that heretofore the lowest incidence of the disease has occurred there in August and September, with the peak being reached in February. This would suggest that the cases previously reported in Winnipeg have been of a different type of disease from that currently prevailing.

It has been reported that the past summer has been unusually warm in Winnipeg, with an abundance of rainfall, and that there has been less activity in mosquito control than in recent prior years.

FINLAND

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

Disease	Cases	Disease	Cases
Diphtheria	112	Poliomyelitis	8
Dysentery	4	Scarlet fever	368
Influenza	1,785	Typhoid fever	51
Paratyphoid fever	105		

MEXICO

Guaymas—Dengue.—Information received from the American Consul at Guaymas, Sonora, Mexico, under date of August 15, 1941, reported an outbreak of dengue in the city of Guaymas and vicinity during the preceding two weeks, with more than 3,000 cases in the city alone. It was stated that the epidemic was abating following control measures instituted by the public health officers, especially the elimination of mosquito breeding.

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