Diphtheria in the United States is in a nonepidemic period and in the Northeast is rare. The study shows that in one urban area where the disease has virtually disappeared, infection with the diphtheria organism is apparently common. Immunity levels and their causes were investigated and are discussed.

DIPHTHERIA: PREVALENCE OF INAPPARENT INFECTION IN A NONEPIDEMIC PERIOD

John P. Craig, M.D., M.P.H., F.A.P.H.A.

DIPHTHERIA offers an ideal object for the study of a formerly epidemic disease which is at present in one of the nonepidemic periods of its cycle. Although sporadic outbreaks continue to occur in the southern and southwestern parts of the United States, it is a familiar fact that diphtheria has become a rarity in the Northeast. New York City, which suffered a mortality rate of nearly 300 per 100,000 in 1875, reported one diphtheria death and only 54 cases during the five-year period, 1956-1960. Unless one assumes that this dramatic disappearance is to be attributed entirely to the use of diphtheria toxoid, it would seem desirable to continue the study of the natural history of diphtheria, especially in times and places where it is rare, if we are to learn anything about the causal factors which determine its prevalence. Frost[1] and Frost, Frobisher, Van Volkenburgh, and Lewin[2] in their studies in Baltimore in the 1920's and 1930's, and later Schuman and Doull[3] in Cleveland, demonstrated very clearly that infection/case ratios could vary greatly in time and place and among different age and ethnic groups. In the decades of 1920-1940 this ratio tended to show a steady rise with the passage of time, yielding progressively fewer cases and deaths for a given number of infections among immunologic susceptibles. One might ask, then, whether it is possible that infection/case ratios in diphtheria could continue to rise toward infinite heights during the evolution of an epidemic cycle, so that persistently high infection rates would yield virtually no cases in certain populations regardless of their previous immune status.

The present study was an attempt to cast some light on this problem by applying old and well-known methods to the current state of affairs in diphtheria, namely, by estimating the current antitoxic immunity status of an urban population in which clinical diphtheria has all but disappeared.

Methods

Diphtheria antitoxin titers in the serums of 1,395 Brooklyn, N. Y., residents, collected in 1957-1958, were estimated by the rabbit intracutaneous method[4] at 0.001, 0.01, 0.1, and 1.0 unit levels. The bulk of the serums from adults were obtained from specimens submitted for routine serologic tests for

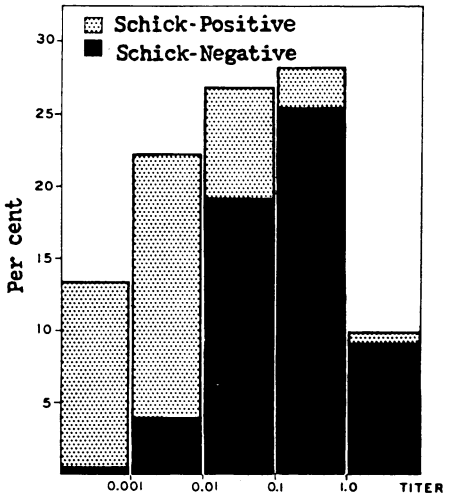

Figure 1—Percentage Distribution of Diphtheria Antitoxin Titers Among 420 Medical Students, Brooklyn, 1956-1958

syphilis either at Kings County Hospital, Brooklyn, or the New York City Department of Health Laboratories. Most of the serums from infants and young children were collected from in- and outpatients at Kings County Hospital.

Estimates of diphtheria antitoxic immunity in earlier periods consisted chiefly of Schick-testing surveys. In order to relate present antitoxin levels to these earlier surveys, the Schick responses and diphtheria antitoxin titers of 420 medical students were compared. The results of this comparison are illustrated in Figure 1. It can be seen that those possessing less than 0.01 antitoxin unit (AU) per ml were predominantly Schick-positive, whereas those possessing 0.01 AU and above were predominantly Schick-negative. The same data are presented in Figure 2 as the per cent Schick-negative at each antitoxin level. These findings confirm the generally accepted statement that antitoxin levels of 0.01 AU/ml or more correspond most nearly to Schick negativity. Exceptions to this are not rare, but the lack of correspondence in each direction tends to be balanced out so that in this group of 420 persons, 64.6 per cent possessed antitoxin levels of 0.01 AU/ml or more, whereas 57.6 per cent were recorded as Schick-negative, a difference of 7 per cent. This is largely accounted for by the fact that nearly 30 per cent of the persons possessing 0.01 to 0.1 unit of antitoxin proved to be Schick-positive with the toxin employed.

Results

The distribution of antitoxin titers of the Brooklyn sample is shown in Table 1. The percentage in each age group possessing 0.01 AU/ml or more is presented in the right-hand column. These data are depicted graphically in Figure 3 by the solid line which represents the percentage in each age group possessing antitoxin levels assumed equivalent to Schick negativity. The open circles connected by the dotted line in Figure 3 represent the per cent Schick-negative reported by Zingher[5] in his survey of about 150,000 New York City residents in 1923.

Antitoxic immunity was consistently greater in children in 1957-1958 than

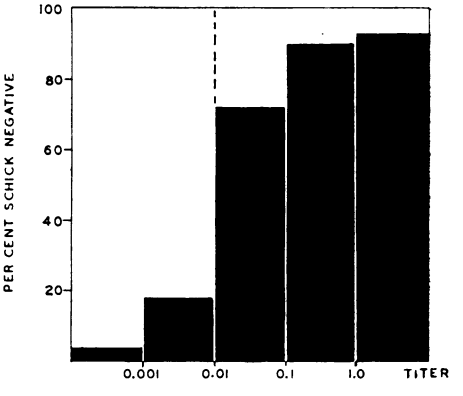

Figure 2—Relationship Between Diphtheria Antitoxin Titers and Schick Response in 420 Medical Students, Brooklyn, 1956-1958

Table 1—Distribution of Antitoxin Titers by Age in 1,395 Brooklyn Residents, 1957-1958

Age	AU/ml					Total	Per cent 0.01 AU or More
	Less than 0.001	0.001-0.01	0.01-0.1	0.1-1.0	Over 1.0		
Less than 1	12	12	8	9	3	44	45.6
1-4	11	9	8	22	21	71	71.8
5-9	6	7	11	25	15	64	79.6
10-14	4	5	15	17	5	46	80.5
15-19	35	41	50	54	17	197	61.4
20-24	41	34	67	81	15	238	68.5
25-29	24	12	36	53	12	137	73.6
30-39	21	9	44	63	26	163	81.6
40-49	22	10	28	50	4	114	71.8
50-59	18	6	28	24	13	89	73.1
60-69	9	11	29	43	9	101	80.2
70-79	12	3	30	46	6	97	84.6
80 and over	4	2	8	19	1	34	82.4
Total	219	161	362	506	147	1,395	72.7

in 1923. The difference is represented by the dotted area, which has most probably resulted from the use of toxoid. After the age of 15, however, 1957-1958 levels are consistently below those of 1923. The cross-hatched area represents the area of difference. It seems likely that the rather rapid fall in adolescence is a consequence of the loss of toxoid-induced immunity gained in childhood. The point worthy of greatest emphasis, however, is that this downward trend appearing in adolescence is not continued into adult life. On the other hand, there appears to be a reversal of the trend resulting in an immunity level roughly parallel to and only 10-20 per cent below that prevailing in 1923, a period of high diphtheria morbidity and mortality. In other words, the important point is not that antitoxic immunity among adults is lower than previously, but rather that it is still so high. The pertinent question seems to be: What are the factors which maintain this high level throughout adult life?

In this connection, it is of considerable interest to compare these results with those obtained by Ipsen and Bowen[6] in 1954 in a similar study of diphtheria antitoxin levels in residents of Massachusetts towns. This comparison is shown in Figure 4. The similarity of the immune status of children under ten in the two areas indicates similar toxoid coverage. The values in adolescence suggest that, if anything, older children were better immunized in Massachusetts than in Brooklyn. Yet the values in Massachusetts fell rapidly after adolescence so that only about 45 per cent of adults over 20 were the equivalent of Schick-negative, whereas a comparable value of 75 per cent was maintained in Brooklyn.

In order to find out more clearly what impact the current toxoid program was actually making in terms of antitoxic immunity in Brooklyn, a more detailed comparison was made of the immune status of infants in 1923 and 1958. The results are shown in Figure 5. Current immunization practice obviously leaves much to be desired since

only 60 per cent of infants have been immunized by the end of their first year. The immunity of newborns in 1958 is consistent with that seen in Figure 3 among adults 20-30 years of age, and properly reflects maternal antitoxin status. Although data from infants below six months of age is not available for 1923, it is clear that passively acquired immunity was at a higher level at that time since the descending portions of the two curves are four to five months apart.

Because of the apparent reversal of the downward trend of antitoxic immunity somewhere between the ages of about 12 and 25, in the Brooklyn study sample, yearly values from age 10 to 29 were determined in order to estimate more precisely when this reversal occurred. These data are shown in Figure 6, expressed both as yearly values and as three-year moving averages. It seems reasonably safe to conclude that immunity begins to fall after the age of 14, remains fairly constant at a level of about 60 per cent Schick negativity from about 15-20, then rises gradually throughout the third decade of life.

To return to the question concerning the probable factors responsible for the maintenance of adult immunity, it seems highly unlikely, for several reasons, that the administration of diphtheria toxoid can be held accountable. In the first place, toxoid was very rarely given to persons over 15 years of age at the time this study was made. Although combined tetanus-diphtheria toxoid for adult use has recently become available, it was not included in the school health programs nor was it used by private physicians in any appreciable quantity until well after 1958. No provision at all is made for giving diphtheria toxoid to adults through city-operated health facilities, and discussion with both health officials and private physicians indicates that virtually no adults have received toxoid in the city even to this date.

Further evidence that toxoid is not responsible for the maintenance of high antitoxic immunity in adults is provided by a comparison of the distribution of antitoxin titers in Brooklyn and Massachusetts which are shown in Figure 7. The four graphs to the left of the dotted line illustrate the distribu-

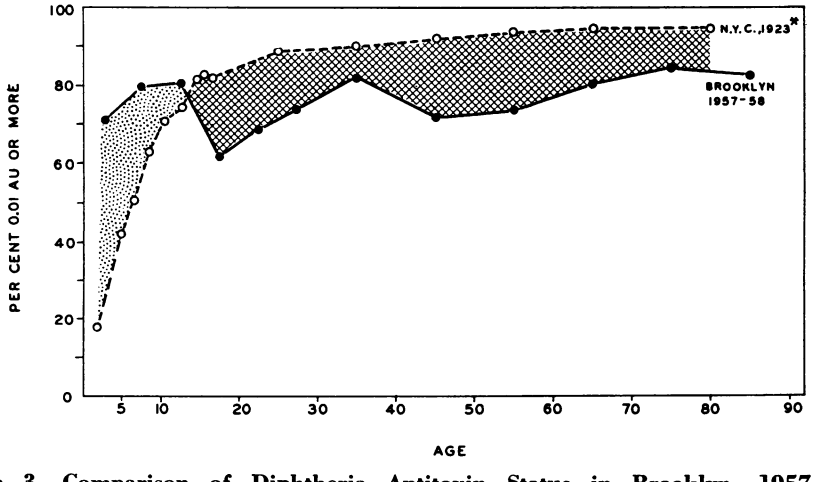

Figure 3—Comparison of Diphtheria Antitoxin Status in Brooklyn, 1957-1958, and New York City, 1923 (after Zingher, 1923*)

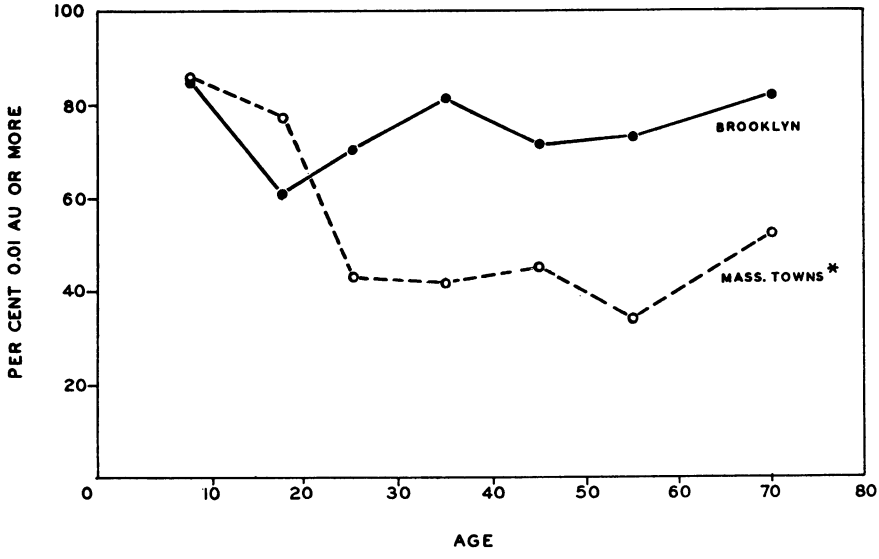

Figure 4—Comparison of Diphtheria Antitoxin Status in Brooklyn, 1957-1958, and Massachusetts Towns, 1954 (after Ipsen and Bowen, 1955*)

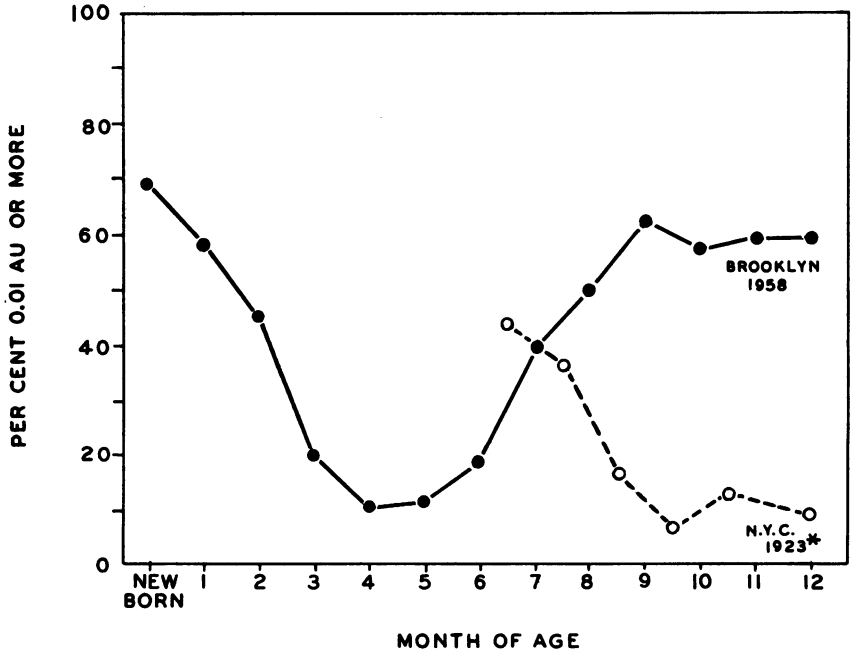

Figure 5—Comparison of Diphtheria Antitoxin Status in Infants, Brooklyn, 1958, and New York City, 1923*

tion of titers in four age groups under 20 in Brooklyn. Titers equivalent to Schick-negative are represented by solid black bars; while titers below 0.01 AU/ml, i.e., those equivalent to Schick-positive, are represented by the dotted bars. The figures above the bars give the combined percentages in each of these two categories. It can be seen that the per cent Schick-negative rises from about 70 per cent in children 1-4 years of age to about 80 per cent in both the 5-9 and 10-14 year age groups, and then falls to about 60 per cent in adolescents. The gradual shift to lower levels and the relatively large percentage in the 0.001-0.01 AU category in the 15-19 year olds is consistent with progressive loss of toxoid-induced antibody. The two graphs to the right of the dotted line show values for Massachusetts towns for the two comparable age groups for which data were available. The graph in the upper right-hand corner showing the titer distribution among first to third grade children again suggests more complete toxoid coverage than in Brooklyn. Those possessing more than 1 AU/ml constitute the largest group. A comparison of the distribution of titers in 15-19 year olds in the two areas, however, reveals that in Massachusetts towns few persons fall into the intermediate category of 0.001-0.01 AU/ml, whereas this category is large in Brooklyn, with the result that 15 per cent fewer persons are Schick-negative in Brooklyn than in Massachusetts. In summary, the differences between these two areas in the age groups under 20 are not great, but such differences as do exist all point to a somewhat higher level of antitoxic immunity in Massachusetts towns than in Brooklyn, most probably as a result of better coverage with toxoid.

When one turns to an examination of adult titers, however, the differences in distribution are very striking, as shown in Figure 8. Not only are there over 30 per cent more persons in the Schick-negative category in Brooklyn, but the proportion of Schick-negatives in the 0.1-1.0 AU band is much greater in Brooklyn than in Massachusetts. The Massachusetts data show clearly, as stated by the authors, that antitoxin titers may in some communities fall

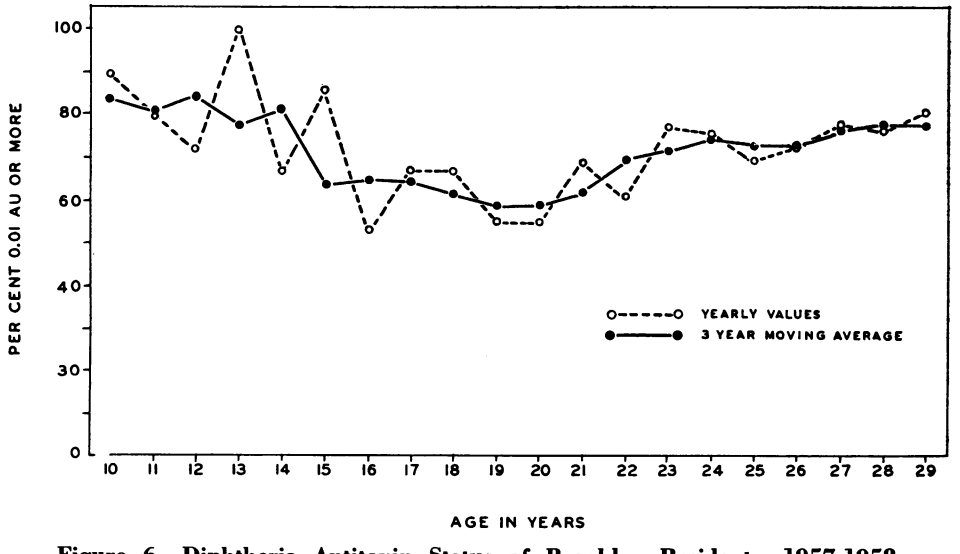

Figure 6—Diphtheria Antitoxin Status of Brooklyn Residents, 1957-1958

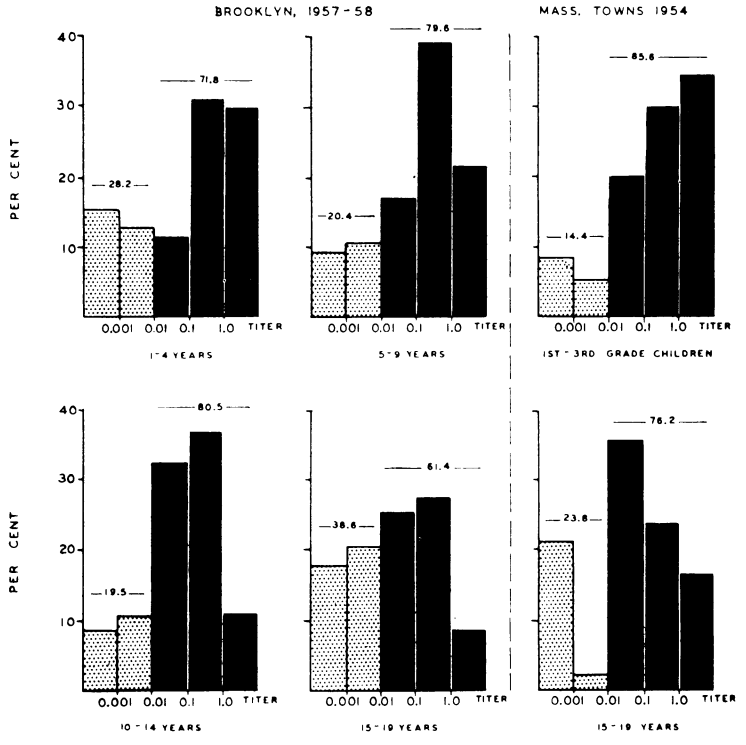

Figure 7—Percentage Distribution of Diphtheria Antitoxin Titers by Age Groups

rapidly with age, even after fairly complete toxoid coverage in childhood, resulting in a largely nonimmune adult population. They attribute this to a marked reduction in natural immunization resulting from the disappearance of the organism from the population.[6] The Brooklyn data would, however, indicate that this is not always the case. Following a toxoid coverage in childhood which, if anything, was less complete than in Massachusetts, adult antitoxin levels in Brooklyn remained high, resulting in a largely immune adult population.

Discussion

Viewing all the data, it would appear that natural infection with toxigenic diphtheria bacilli is by far the most likely factor responsible for the high level of immunity in Brooklyn adults. In fact, in view of the rather minor differences between adult antitoxin levels in New York City in 1923 and Brooklyn in 1957-1958 (Figure 3), it is likely that the frequency of infection today is not far below that of 1923. Therefore, whereas infection may at present be rare in some communities, which seems to be the case in Massachusetts towns, the results of this study would indicate that it is still common in at least one urban area where the disease has virtually disappeared.

If it is accepted that inapparent infection is a frequent event in Brooklyn, then the absence of disease cannot reasonably be attributed to absence of infection. In fact, the occurrence of 29 cases of diphtheria in the past five years

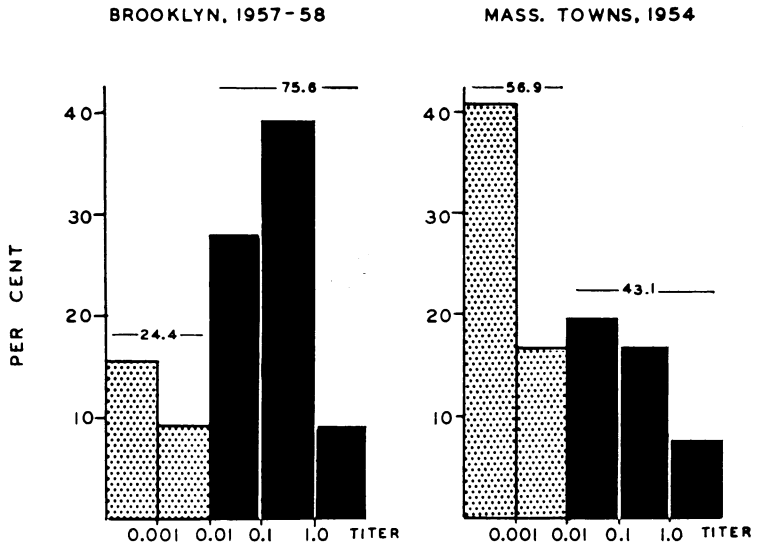

Figure 8—Percentage Distribution of Diphtheria Antitoxin Titers in Adults 20 Years of Age and Over (after Ipsen and Bowen, 1955)

attests to the fact that infection is endemic, although disease is extremely rare. Moreover, since some 20-25 per cent of Brooklyn children under 15 are Schick-positive, of whom at least half possess no detectable antitoxin whatsoever, the absence of disease cannot be attributed to a lack of immunologic susceptibles. It follows, therefore, that the virtual disappearance of diphtheria cannot reasonably be attributed to immunization with diphtheria toxoid, although by reducing the number of immunologic susceptibles, toxoid has undoubtedly contributed in part to the decline. This interpretation of the facts is, of course, not new, but the present study simply adds confirmatory evidence to earlier assessments of the role of active immunization in the decline of diphtheria.[2,3,7]

It appears, then, that at the present time a very high infection/case ratio must exist even among immunologically susceptible children, unless one is to assume that immunizing infections are occurring only in adults. The use of the term infection/case ratio is, of course, an expression of our ignorance, for the factors which determine this ratio in a given time and place remain unknown. It is possible that secular changes are determined largely by elimination of the biologic susceptibles during the early period of the epidemic cycle when fatality rate is relatively high. On the other hand, immunity to the somatic antigens of the diphtheria bacillus and related Corynebacteria may play a hitherto unrecognized role in the epidemiology of diphtheria. It was with this latter thought in mind that the present study was conducted, and with this as a prelude, these studies are now under way.

REFERENCES

1. Frost, W. H. Infection, Immunity and Disease in the Epidemiology of Diphtheria. With Special Reference to Studies in Baltimore. J. Prev. Med. 2:325, 1928.
2. Frost, W. H.; Frobisher, M., Jr.; Van Volkenburgh, V. A.; and Levin, M. L. Diphtheria in Baltimore:

A Comparative Study of Morbidity, Carrier Prevalence and Antitoxic Immunity in 1921-24 and 1933-36. Am. J. Hyg. 24:568, 1936.
3. Schuman, L. M., and Doull, J. A. Diphtheria Infection and Morbidity in Cleveland, 1937-1939. A.J.P.H., Suppl. 30:16 (Mar.), 1940.
4. Jensen, C. Die Intrakutane Kaninchen Methode zur Auswertung von Diphtherie Toxin und Antitoxin. Acta path. et microbiol. Scandinav. 10: Suppl.:14, 1933.
5. Zingher, A. The Schick Test Performed on More than 150,000 Children in Public and Parochial Schools in New York (Manhattan and Bronx). Am. J. Dis. Child. 25:392, 1923.
6. Ipsen, J., and Bowen, H. The Effects of Routine Immunization of Children with Triple Vaccine (Diphtheria, Tetanus, Pertussis). A.J.P.H. 45:312, 1955.
7. Pascua, M. Evolution of Mortality in Europe during the Twentieth Century. WHO Epidemiological and Vital Statistics Report 4:36, 1951.

Dr. Craig is assistant professor of microbiology and immunology, Department of Microbiology and Immunology, Downstate Medical Center, Brooklyn, N. Y.

This paper was presented before the Epidemiology Section of the American Public Health Association at the Eighty-Ninth Annual Meeting in Detroit, Mich., November 14, 1961.

This investigation was supported in part by a research grant from the Institute of Allergy and Infectious Diseases, National Institutes of Health, Public Health Service.

The Fallout Protected Hospital Called Feasible

"Fallout Protection for Hospitals," PHS Publication No. 791 (Revised), presents the findings of a special study to develop principles for hospital design offering protection from effects of gamma radiation resulting from nuclear explosion fallout. Issued earlier in preliminary form under the title "Prototype Hospital—Fallout Protected," this latterly published 28-page report discusses the feasibility of designing fallout-protected hospitals. A 150-bed hospital, the report indicates, would cost about 4 per cent more if fallout-protected than a hospital of so-called conventional construction. Another 2 per cent would also provide protection against chemical and biological contaminants and against a "moderate blast." Text is illustrated by floor plans and other diagrams. Government Printing Office, Washington 25, D. C.; 30 cents.