Laboratory Problems in the Control of Meningococcus Meningitis*

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OUTBREAKS of meningococcus meningitis offer adequate evidence of the futility of the control measures which have been employed, and the literature gives slight promise of the immediate development of effective control measures which can be generally applied. Carriers have commonly been considered more important in the transmission of the disease than cases, yet carrier surveys, as usually carried out, have complicated the administrative problems involved without aiding materially in control. The carrier incidence in a group may run above 35 per cent and the outbreak abate without their segregation. In other instances, the segregation of carriers, as found, has had no influence on the course of the outbreak. As a result of such observations the wholesale meningococcus carrier survey has fallen into disrepute, probably to the best interests of all concerned.

The wholesale carrier survey has, at least, served to emphasize the fact that there are many problems in the bacteriology, infection, immunity, and epidemiology of meningococcus meningitis which have not been worked out or have been ignored in routine work. The responsibility for improvement in methods of control rests squarely on the laboratory, and if any success is to be attained the laboratory worker must approach each outbreak as an applied research problem rather than with the aim of getting the largest number of carrier cultures made in the least possible time. This premise justifies this incomplete presentation of certain theoretical phases of the subject and the fragmentary observations cited as offering possibly some basis or stimulus for studies on the epidemiology of the disease.

No small part of the confusion which exists arises from attempts to evaluate observations and findings on the same basis as is used in considering the more highly communicable diseases. A meningococcus meningitis outbreak cannot be compared with a typhoid outbreak and a meningococcus carrier does not have the same epidemiological significance as a typhoid carrier. A better understanding of the problem may be obtained by a classification of communicable diseases which divides them into those of universal susceptibility and definite epidemiology and those of limited susceptibility and obscure epidemiology.

I. DISEASES OF UNIVERSAL SUSCEPTIBILITY AND DEFINITE EPIDEMIOLOGY

Typhoid fever, smallpox, mumps, and measles offer examples of diseases

* To be read before the Laboratory Section of the American Public Health Association at the Sixty-fifth Annual Meeting in New Orleans, La., October 21, 1936.

of universal susceptibility and definite epidemiology, to which, as a group, the following characteristics may be ascribed:

A. Causative organisms are aggressive invaders of the body, regardless of the severity of the symptoms produced when an invasion has been accomplished.

B. Populations are universally susceptible, unless naturally or artificially immunized.

C. Susceptibility is not related to a lowered general resistance.

D. The carrier level is relatively low in those in which carriers are known to exist.

E. Carriers are almost universally a menace.

F. Cases are usually referable to a known preceding case or carrier.

G. Clinically mild and atypical cases are much less common than in the second group.

H. Control measures are fairly well established.

II. DISEASES OF LIMITED SUSCEPTIBILITY AND OBSCURE EPIDEMIOLOGY

Meningococcus meningitis, poliomyelitis, the pneumonias, and undulant fever are examples of this group, and as a result of extensive immunization diphtheria also may possibly be included in this group. The chief characteristics of the group are:

A. Causative organisms are not aggressive invaders of the body. Virulence involves at least 2 factors: the aggressiveness of the organism as an invader, and the ability to produce severe symptoms when an invasion has been accomplished. These 2 factors are well correlated in diseases of universal susceptibility, but the correlation is not so marked among the diseases of limited susceptibility. The meningococcus is ordinarily a poor invader at best, but even the poorest invaders among the meningococci may attack with much fury when, through some combination of circumstances, an invasion has been accomplished.

B. Only a limited portion of the population is susceptible. If the intradermal skin test with meningococcus toxin, adjusted by tests on newly developed cases of meningococcus meningitis, is a reliable index, findings bear out this statement. The writer has made 626 such tests on institutional and residential populations among which cases of meningococcus meningitis had occurred. On the basis of the edema and erythema produced, 25.7 per cent were slightly susceptible and 1.5 per cent were highly susceptible. Younger groups showed a greater susceptibility than older.

C. A lowered general resistance is usually essential to an invasion by organisms of average virulence, even in the susceptible group. Case histories in meningococcus meningitis usually reveal some predisposing factor which has tended to lower the resistance of the individual. These include upper respiratory infections, otitis media, gastrointestinal upsets, extreme and prolonged fatigue, prolonged exposure to inclement weather, the excessive use of alcohol, and numerous less easily detected causes.

D. The carrier level is relatively high in diseases in which carriers are known to exist. Several instances have been reported in which the meningococcus carrier incidence exceeded 50 per cent. Glover [1] considers that when the carrier level reaches 20 per cent, the community is in danger of an outbreak of meningitis.

E. Carriers are not universally a menace. Effective meningococcus carriers are probably few in number. One error in the carrier survey has been a lack of understanding of the fact that there are epidemic, non-epidemic or sporadic, and probably saprophytic strains of the meningococcus, similar in characteristics to those reported among the pneumococci. This grouping fits in nicely with the generally accepted type classification of meningococci. The actual epidemiological basis for the classification is that phase of virulence which has to do with the aggressiveness of the organism as an invader of the

deeper tissues. Rake [2] groups meningococci on the basis of Gordon's classification:

Type I–III: Parasitic or epidemic and responsible for nearly all the large epidemics and most of the small ones.

Type II: Normally a saprophyte, frequently present in the throats of normal individuals. Can also act as a parasite and produce sporadic cases of the disease and even limited epidemics.

Other types: Saprophytes, present in the throats of normal individuals where they seem to cause no harm. Only occasionally do they cause a sporadic case of meningitis.

In general, the carriers of non-epidemic and saprophytic strains of the meningococcus are more consistently positive on repeated culture and the condition is of longer duration than is the case with carriers of epidemic strains. The non-epidemic and saprophytic strains are more easily grown than are the epidemic strains. It seems likely, then, that most of the carriers detected in routine carrier surveys have been of no epidemiological significance.

The dangerous carrier of epidemic strains is frequently of the chronic, intermittent type, capable of transmitting massive infections at times but with intervals when the meningococcus is apparently not present in the superficial tissues of the posterior nasopharynx. An individual may be able to resist the attack of a few poor invaders but succumb to a large number of these same organisms when his general resistance has been lowered by some predisposing factor. Limited studies on chronic, intermittent carriers of epidemic strains have shown that individuals may yield practically pure cultures of meningococci at times, while at other times few or none are found.

This intermittent character of effective carriers is one factor which contributes to the baffling epidemiological picture often observed and accounts, in some instances at least, for the failure of the carrier survey. The writer [3] has reported a carrier of Gordon Type I–III meningococci who appeared to have been responsible for 5 cases in an institution, distributed over a period of about 9 months and who continued to give an occasional positive culture for 5 months more. Rake [4] has reported carriers of this sort in which repeated cultures were negative for periods of several months, after which positive cultures were again obtained. The unreliability of the usual regulations for the release of carriers becomes apparent in the light of such findings.

Since the inference has been made that the technic commonly used in carrier surveys may not always detect the dangerous carriers, a word regarding technic may not be amiss. The technic which gives some assurance of isolating and identifying the less easily cultivated epidemic strains of the meningococcus, lends itself better to an intensive and prolonged study of a carefully selected group than to a single culturing of an extensive group selected by administrative order or in a haphazard manner. The writer has set an arbitrary, maximum limit of 40 cultures per day when working alone in the field, and this may be too high for best results. Space does not permit a detailed description of the technic involved, and the reader is referred to the excellent outline of the subject by Branham [5] for further information. Certain points will bear emphasis, however: (1) There are no reliable shortcuts in technic, such as the use of Olitsky's medium; (2) the identification of freshly isolated strains of the meningococcus cannot always be safely based on agglutination reactions, to the exclusion of carbohydrate fermentation; (3) typings must be made, without exception, if the findings are to be of any epidemiological significance.

F. Cases are not usually referable to a preceding case or carrier, as found. This statement holds true in the ma-

jority of meningococcus meningitis outbreaks. Painstaking and detailed epidemiological investigations have led on several occasions to the selection of a small group which, upon repeated culturing, has yielded a chronic intermittent carrier who fitted into the epidemiological picture and whose removal coincided with the end of the outbreak.

G. Clinically mild and atypical cases are very common and may exceed the clinically typical cases in number. Ordinarily only meningococcus infections involving the meninges are recognized; yet there is considerable evidence that a meningococcus septicemia always precedes the meningitis, and meningococcus septicemias without meningeal involvement have been repeatedly reported. Meningococcus meningitis following sinus involvement occurs frequently enough to suggest that the meningococcus may be the causative organism in many sinus infections, rather than a secondary invader. Upper respiratory infections are also numerous during an outbreak of meningococcus meningitis. Are these the usual run of respiratory infections or are these individuals suffering from a mild form of local meningococcus infection as has been suggested by Mink [6] and others.

Certainly meningococcus infections without meningeal involvement offer greater opportunities for the dissemination of the parasitic types of organism than cases of meningitis, and considerable study may well be devoted to the problem.

H. Control measures are not as well established as in the group of diseases of universal susceptibility. The measures used with the first group of diseases are employed as a matter of form, but the special measures which have proved slightly more effective are those which contribute to the maintenance of a high level of general resistance in the individual.

These characteristics of diseases of limited susceptibility and obscure epidemiology cast some light on the problems involved. Outbreaks will be cited as illustrative of some of these points and extensive observations along these lines may give some information of value in the control of the disease.

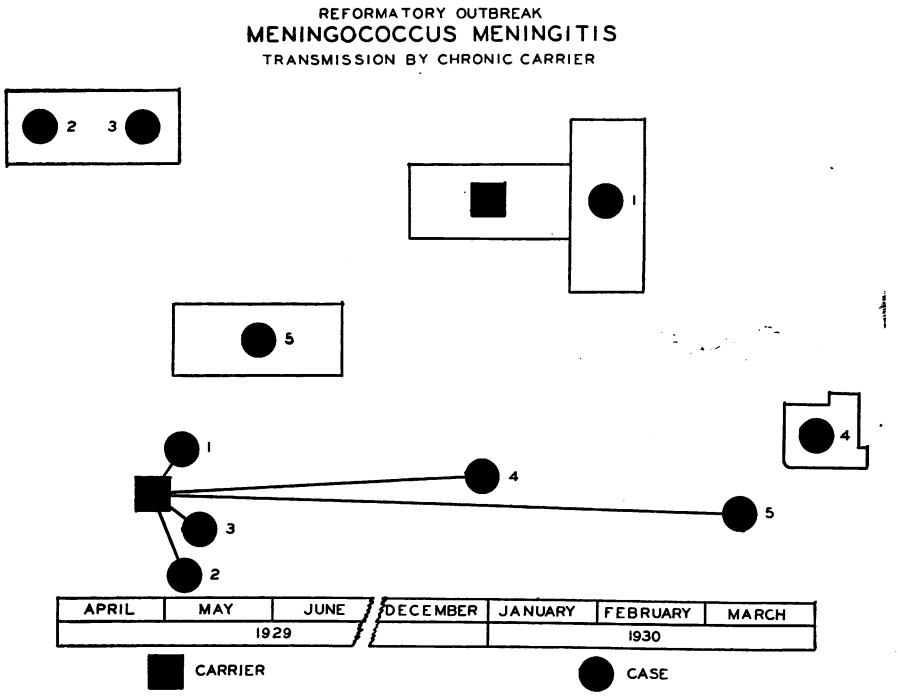
Some mention should be made of the use of meningococcus toxin. The production of meningococcus toxin by Ferry, Norton, and Steele [7] has introduced the possibility of its use for intradermal skin tests, as an index of immunity, and for artificial immunization. Kuhns [8] and the writer have both done some work along these lines but extensive use and prolonged observation will be necessary before definite conclusions may be drawn.

The almost universal observation of a lowered general resistance as a predisposing factor for the development of cases of meningococcus meningitis, involving organisms of average virulence, suggests that the intradermal skin test may only give an index of one of several factors concerned in susceptibility to the disease.

Limited experience with the use of raw meningococcus toxin as an immunizing agent also indicates that the amount which can be injected without causing severe reactions is not sufficient to produce as high a degree of immunity against the intradermal skin test as is desirable. There are also some observations that suggest that the use of meningococcus toxin may only immunize against certain minor clinical symptoms, similar to what has been alleged in connection with the immunization against scarlet fever with streptococcus toxin.

These statements are not intended as a criticism but as a caution against over-enthusiasm and inadequately supported claims. The only communicable diseases which may really be considered as controllable are those for which an easily used, active immunization has

FIGURE I



been developed. For meningococcus meningitis, whether this be meningococcus toxin, an autolyzed meningococcus filtrate or some other product, studies aimed at the production of an effective agent for active immunization seem to offer the greatest promise of successful control of the disease.

The following outbreaks of meningococcus meningitis serve to emphasize certain of the characteristics of the disease which have been outlined above.

1. REFORMATORY OUTBREAK

This outbreak occurred in a state reformatory with about 650 inmates and 50 officers and their families.

Figure I shows both the geographical and chronological distribution of cases. Five cases occurred, 3 among officers (Cases 1, 4, and 5) from 35 to 67 years of age, and 2 among inmates (Cases 2 and 3) under 21 years of age. Wholesale carrier surveys, made after the development of both the 3rd and 4th cases, were of no value in control.

The organism involved in the last 2 cases was identified as a Gordon Type I–III meningococcus and it was assumed that there was probably a chronic carrier of this organism either among the officers or their families, since 3 of the 5 cases had been officers. The next culturing was limited to officers, their families, and "H" Company, the last case having been the captain in charge of "H" Company.

No carriers of Type I–III meningococci were found among the officers or their families, but one member of "H" Company, who had given negative cultures on both the wholesale carrier surveys, gave practically a pure culture of meningococcus which could not be distinguished from those isolated from the spinal fluid of the last 2 cases. The relation of this carrier to the cases was as follows:

April 25, 1929—Carrier committed to the reformatory, assigned to "H" Company and detailed to the rock quarry force.

May 4, 1929—Case 1 (the captain in charge of the rock quarry force) developed meningococcus meningitis. He was a robust individual, apparently in the best of health, who had returned from a week's spree on April 27, 2 days after the carrier entered the reformatory. In the 2 or 3 days after his return to duty, he had helped the carrier lift heavy rocks. The explosive exhalation of breath while under the strain of this work had given ample opportunity for droplet infection.

May 8, 1929—Case 2 ("G" Company) developed meningococcus meningitis. He was also assigned to the rock quarry force and had been a friend of the carrier before entering the reformatory. He was an undernourished individual who had contracted a severe cold about 3 days prior to the appearance of meningeal symptoms. Ample opportunity for infection was given both at work and through the practice of passing a pipe from mouth to mouth while on the recreation grounds. Case 3 also participated with these 2 in this practice.

May 13, 1929—Case 3 ("G" Company) developed meningococcus meningitis. Occupied the bunk next to Case 2 in quarters and was a close associate of both the carrier and Case 2. He was undernourished, anemic, and was noted for repeated admittances to the infirmary on diagnosis of hysteria.

December 26, 1929—Case 4 (Superintendent of the reformatory) developed meningococcus meningitis. He was an obese, elderly individual who had lost 20 lb. in the month prior to the development of meningitis as a result of a severe, protracted cold and the worries incident to assuming management of the reformatory.

The carrier had escaped from the institution and upon his return was required to report in person to the superintendent daily. The superintendent made it a practice to get extremely close to those with whom he conversed, thus increasing the opportunities for droplet infection. He developed the disease 7 days after his first interview with the carrier.

March 7, 1930—Case 5 (the captain in charge of "H" Company) developed meningococcus meningitis. He had had a severe gastrointestinal upset a few days before. He probably acquired his infection when he forced the carrier against the wall and choked him, in quelling a disturbance in quarters 6 days prior to the onset of his illness.

This carrier was cultured at frequent intervals over 5 months. The majority of cultures failed to show meningococcus. An occasional culture showed a few meningococcus colonies and twice almost pure cultures were obtained, establishing his status as a chronic, intermittent carrier capable at times of transmitting massive infections.

The writer [3] has reported a similar outbreak in a state penitentiary, involving a Gordon Type I meningococcus. Wholesale carrier surveys were of no value in control and the geographical and chronological distribution of cases was similar to the reformatory outbreak. Epidemiological studies revealed that all the cases had occurred among skilled men in the building trades who worked together on construction jobs about the prison. Careful culturing of the remainder of this limited group revealed a chronic, intermittent carrier who was quartered in a cell house where no cases of the disease had developed. As with the reformatory outbreak, the institution was free from meningococcus meningitis for a number of years following the removal of the chronic carrier.

These outbreaks emphasize the following points:

A. Carriers of sporadic and saprophytic types of the meningococcus are of no epidemiological significance in outbreaks.

B. The dangerous carrier is of the chronic, intermittent type who is harboring an epidemic strain of the organism and who is capable of transmitting massive infections at times.

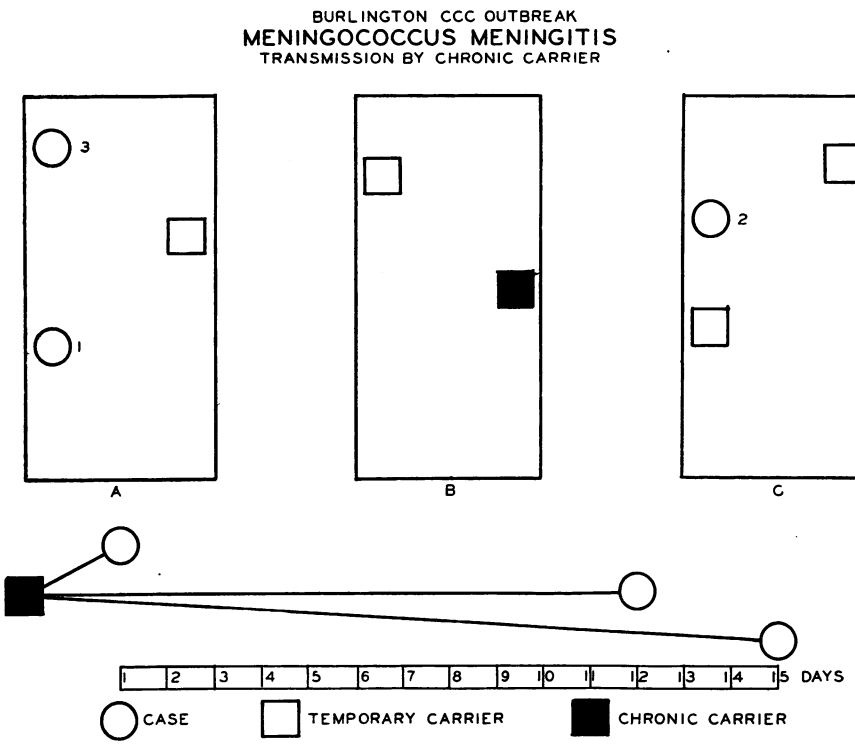
C. A lowered general resistance of the individual, coupled with a massive infection is essential for a successful invasion by meningococci of average aggressiveness.

D. Careful epidemiological studies may be of value in selecting the group which includes the effective carrier.

2. BURLINGTON CCC OUTBREAK

This outbreak occurred in a Civilian Conservation Corps Camp at Burling-

FIGURE II



ton, Kan., in November and December, 1935. The personnel of the camp included over 200 enrollees, officers and supervisors who were quartered in cantonment type barracks.

Figure II shows the chronological distribution of cases and their location in barracks. Three cases occurred at intervals of 12 and 3 days, respectively, among enrollees. Two cases (Cases 1 and 3) were quartered in Barrack A, and 1 case (Case 2) in Barrack C. Typings were not entirely satisfactory because of broad agglutinations and absorptions, but somewhat better results were obtained with Type III sera than with other types and the organism was considered an epidemic type.

Preliminary epidemiological investigations gave no significant leads and it was decided to culture the entire camp personnel in groups of a size in which it would not be necessary to sacrifice accuracy of technic to speed. Thirty-one, or 14.2 per cent, of the 217 persons cultured were found to be meningococcus carriers.

This was the first outbreak handled by the writer in which he had the courage of his convictions as regards the carriers of epidemic and non-epidemic strains of the meningococcus. Of the 31 carriers identified, 26 yielded non-epidemic or saprophytic strains and 5 epidemic strains. Only the 5 carriers of epidemic strains were isolated. One of these 5 carriers, quartered in Barrack B where no cases of the disease had developed, proved to be a chronic, intermittent carrier of an organism which closely resembled those recovered

from 2 cases. He had been closely associated with the 2 patients either in tussles or contests of strength and skill prior to their illness, which may account for their infection.

The writer had charge of this outbreak which Kuhns [8] has cited as an example of successful control through the use of meningococcus toxin for immunization, in which opinion the writer does not concur. Skin tests for susceptibility were read jointly by the camp surgeon and the writer on December 5, the day that the carriers of epidemic strains of meningococci were isolated. No new cases developed between December 5 and December 20, when the 4th dose of meningococcus toxin was given to the 89 skin test reactors among the camp personnel. Certainly the toxin cannot be given credit for the prevention during a considerable portion of the immunization period. This absence of cases may be due to the vagaries of the epidemiology of the disease, but the whole outbreak so closely resembles those of the reformatory and penitentiary mentioned above, as well as others in the writer's experience, where removal of chronic intermittent carriers of epidemic types of meningococci has coincided with the end of the outbreak, that this fact cannot be ignored.

3. SPEARVILLE CARRIER

The history of this carrier presents some interesting possibilities both as to the duration of the chronic carrier state and the production of cases by carriers of non-epidemic or sporadic strains of the organism.

The mother of a family of 11 children, residing on a large wheat farm, had meningococcus meningitis in 1928 and recovered. Since that time, 3 of her 11 children have developed the disease: 1 case, fatal, in February, 1930, 1 which recovered, March, 1930, and 1 which recovered in March, 1936.

Cultures made early in June, 1936, revealed the fact that both the mother and her 3 year old daughter were carrying a Gordon Type II (sporadic) meningococcus which had rather broad cross-agglutination and absorption reactions with both Types I and III sera.

The number and distribution of cases suggests that this woman has been a chronic, intermittent carrier of a non-epidemic strain of meningococcus since her recovery in 1928. A culture made in August, 1936, was negative, and additional studies will be made.

Skin tests made with polyvalent meningococcus toxin in June, 1936, gave negative reactions on the mother and the 2 children who have had the disease. Of the remainder of the family, 5 gave 1 + skin tests, 1 a 2 + test and 1 a 4 + test. The 4 + test is comparable to the skin test susceptibility of newly developed cases of the meningococcus meningitis which have been tested. These results suggest that other factors than skin test susceptibility are more important than the skin test in the transmission of the disease.

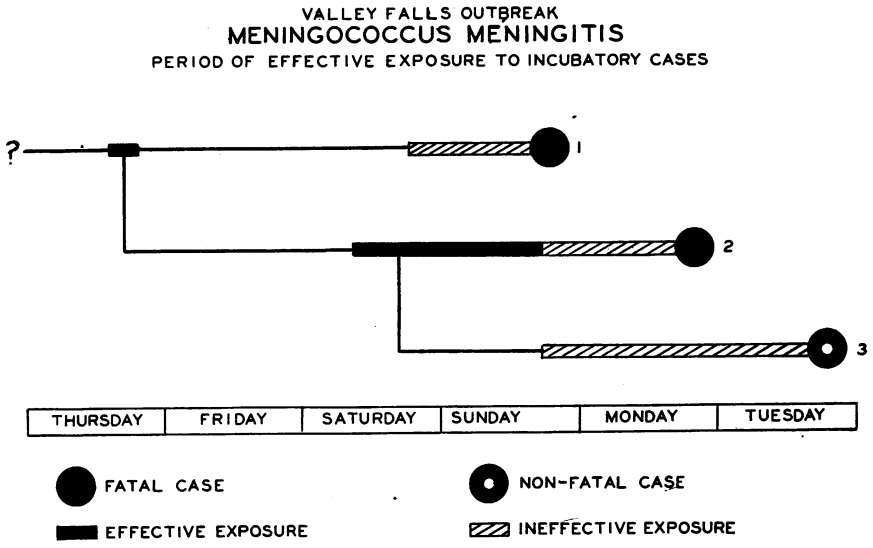
Transmission of meningococcus meningitis by clinical cases of the disease has not appeared to be as common as transmission by carriers. The following outbreaks illustrate the usual and exceptionally rare types of transmission by cases:

4. VALLEY FALLS OUTBREAK

Three cases developed on successive days, 2 were high school students and the 3rd a sister of the 2nd patient, was a grade school pupil (Figure III).

The source of infection in the first case is not known, but in view of the rather definite incubation period in Cases 2 and 3, the patient probably acquired his infection either Wednesday night or Thursday morning. Case 2 acquired his infection from Case 1 while returning from a basket ball game

FIGURE III



in an open truck. The 2 boys became chilly during the 20 mile trip and put their heads together under a blanket, giving ample opportunity for transference of the organism from Case 1, then in the early incubation stage. Patient 3 was the sister of patient 2 and was at home with her brother during the early stages of his incubation period. A culture of Case 2 taken a few hours before the development of clinical symptoms failed to show the presence of meningococci.

Each of these patients was in contact with several children in their respective families during that stage of the incubation period just prior to the development of clinical symptoms and no cases resulted, while exposures during the early stages of the incubation period were productive of cases. All of the children exposed were suffering from severe colds with laryngeal involvement, which would be considered a predisposing factor to infection, yet cultures taken shortly after the development of cases showed no meningococci.

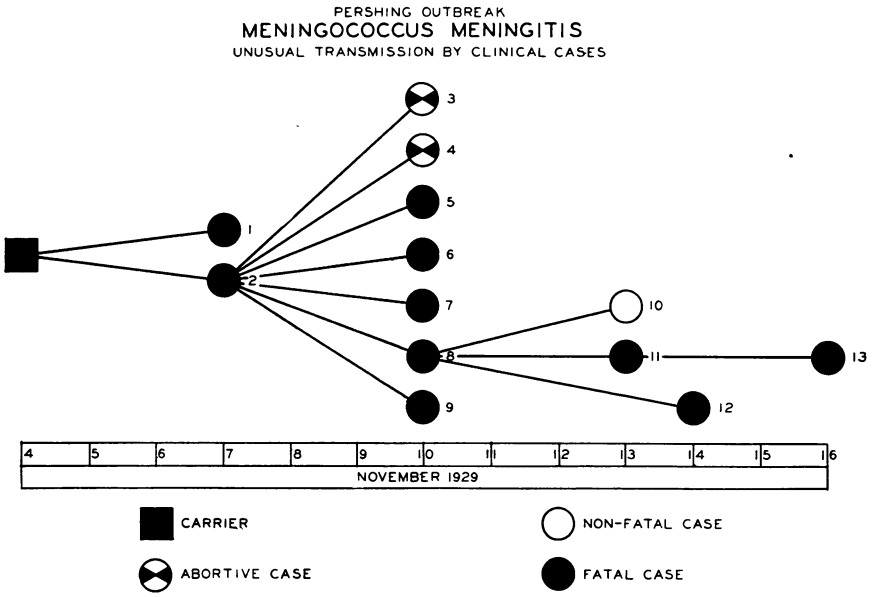
This illustrates the common observation that clinical cases are most infectious during the first 24 or 36 hours of the incubation period when large numbers of meningococci are present in the posterior nasopharynx and massive infections can be transmitted. In most instances the organisms enter the deeper tissues and disappear from the nasopharynx before the appearance of clinical symptoms, and the case is no longer infectious.

5. PERSHING OUTBREAK

This has been reported [3] but is briefly presented because it graphically shows the rather unusual transmission of the disease by fulminating cases after clinical symptoms have developed. This outbreak was due to a Gordon Type I organism of exceptional aggressiveness as an invader.

Figure IV shows the chronological grouping of cases and sources of infection. Most of the cases were persons of middle age, the incubation period was 3 days, and most of the patients died in from 11 to 14 hours after the appearance of the initial symptoms. A total

FIGURE IV



of 23 persons were exposed to these cases during the clinical stages, 11 of whom developed the disease.

While such effective transmission will not ordinarily be encountered, the possibility must be considered in fulminating outbreaks of the disease. While such outbreaks are spectacular and terrifying, they offer a much simpler problem of control than the usual type.

SUMMARY

The theories presented and outbreaks cited cast some light on the problems involved in the transmission of meningococcus meningitis and somewhat similar studies may be of material assistance in the development of methods of control of the disease.

Studies dealing with the following problems are suggested:

A. Epidemiological significance of what have been termed epidemic, non-epidemic, and saprophytic strains of the meningococcus.

B. The prevalence and epidemiological significance of meningococcus infections other than meningitis.

C. The epidemiological relationships of chronic, intermittent carriers to sporadic cases and outbreaks of meningococcus meningitis.

D. Improvement in the technic of culturing meningococcus carriers.

E. Predisposing factors to meningococcus infection.

F. The development of reliable and easily applied tests for immunity to meningococcus meningitis as well as effective methods of immunization.

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