CUTANEOUS ALLERGY IN GONOCOCCAL INFECTIONS.*

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The inoculation of the gonococcus into the body of man or animals causes changes in the blood which have been demonstrated by studies of the specific agglutinins, precipitins, and opsonins. More recently the antibody content of the serum has been estimated by means of complement fixation, using preparations of the gonococcus as antigen. By all these methods, the variations in the course of gonococcal infection may be more or less satisfactorily followed, and, in the case of the opsonins at least, the curve of immunity may be correlated with the changes in the clinical course of the disease.

Certain reactions, also, follow the subcutaneous inoculation of suspensions of killed gonococci in patients suffering from gonococcal infection. These reactions are characteristic[†] and are analogous to those seen after the injection of tuberculin, mallein, etc., in the respective diseases. At the site of the inoculation there appears after a few hours, an area of redness, swelling, and tenderness, from 2 cm. to 6 cm. or more in diameter, depending upon the amount of the suspension inoculated. Sometimes the whole upper arm becomes swollen and painful. After 24 to 48 hours the reaction subsides. There is frequently an increase in pain and sometimes swelling in the affected joints or other localizations, together with general symptoms of malaise, headache, and fever. An increase in leukocytosis may occur.

The degree of the reaction varies in different cases with the extent of the infection and the general condition of the patient. In gonococcal arthritis in which active symptoms have been absent for some time, a subcutaneous inoculation may produce little more than a local reaction at the site of the injection. In chronic types of arthritis in which there have been repeated severe attacks of the

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† *Jour. Infect. Dis.*, 1908, 5, p. 270.

infection, the reaction may be very slight or absent. These cases often do badly under vaccine treatment. In cases in which repeated inoculations are made for therapeutic purposes, the reactions usually grow less with successive doses of the same size. Patients who have received a number of inoculations of moderate doses, without exhibiting more than a slight reaction, occasionally show a pronounced reaction after an inoculation of the same size, given in the same way as previous doses.

Ocular reactions following inoculations are sometimes observed in cases in which iritis has previously been present. A man of 35 who had suffered from arthritis and iritis six years previously complained of pain in the joints of the spine and ankles. There had been no recent active trouble in the eye. He was given a subcutaneous inoculation of 100 million gonococci for diagnostic purposes. Twenty-four hours later the previously affected eye became painful: photophobia and some conjunctival injection were present. The other eye showed no change. The symptoms subsided after 24 hours. Reactions characterized by increased inflammation, or by effusions in the eye, are not infrequent after therapeutic inoculations of vaccine in active gonococcal iritis. In a number of cases, however, such reactions have been entirely absent, even after large doses of vaccine.

The degree of reaction depends not only on the number of gonococci inoculated, but also on the source and age of the cultures from which the vaccine is prepared. Recently isolated cultures (two weeks to three months, fifth to 40th generation) furnished a vaccine 10 times as strong as a culture which had been grown in the laboratory for two years. This variability in the activity of vaccines may explain the differences of opinion as to the optimum therapeutic dose of gonococcal vaccine.

The reaction has a diagnostic value in obscure cases of arthritis, and its use has also been suggested for the determination of the cure of local gonococcal infections. Bruck¹ has observed the reaction in epididymitis, and Reiter² in pelvic infections in women, and in arthritis.

¹ *Deutsche med. Wchnschr.*, 1909, 35, p. 470.

² *Ztschr. f. Geburtsh. u. Kinderh.*, 1911, 68, p. 471.

CUTANEOUS ALLERGY.

The cutaneous reaction to injections of preparations of the gonococcus has been studied by several workers. Bruck¹ obtained a "cutireaction" by intradermal inoculation of gonococcal vaccines. Köhler² inoculated, by the method of von Pirquet, vaccines prepared from streptococcus, gonococcus, colon bacillus, etc., and was able to demonstrate the specificity of the reaction in cases of gonococcal infection.

In recent experiments with glycerin extracts of the gonococcus, I have found that a well defined cutaneous reaction, similar to the cutaneous tuberculin reaction, occurs in cases of gonococcal infection, when the extract is introduced into the skin by the method of von Pirquet, and that the course of the immunity curve in a given case may be traced from day to day by noting the degree of the reaction after successive inoculations. These curves are similar to those obtained by daily estimations of the opsonic index, and their fluctuations may be correlated with the clinical changes observed in the patient. In recently infected cases, the cutaneous allergy is seen to increase steadily from day to day.

PREPARATION OF MATERIAL FOR TESTS OF CUTANEOUS ALLERGY.

Cultures of strains of the gonococcus were grown on ascites agar for 24 hours, the growth removed with sterile distilled water, 0.5 per cent phenol added, and the suspensions placed at 37° C. for 48 hours. The fluid was then heated to 60° C. for two hours, glycerin added, and the mixture evaporated in a current of warm air. The final product was a clear yellowish fluid of the consistence of glycerin. In the following discussion it will be referred to as "gonococcin" in conformity with the terminology of other similar products, such as tuberculin, leprolin, tricophytin, luetin, etc.

The technic briefly described has been modified in various ways in the course of the work, without essentially changing the results. Human blood agar as a culture medium was substituted for ascites agar without changing the action of the final product. No difference was noted in the products when normal salt solution was used

¹*Loc. cit.*

²*Wien. klin. Wchnschr.*, 1911, 24, p. 1564.

in place of distilled water for making the suspensions, and the latter was adopted to avoid the possible irritant action of the salt in the concentrated product.

Material for control inoculation was prepared in precisely the same manner, using the washing from the same number of uninoculated culture tubes.

Cultures from five strains of gonococci were combined in the antigen used in most of these cutaneous tests. Experiments with antigens made from single strains showed that in some instances the reaction from one of the strains was less than that from the others. The strains used were derived from cases of arthritis and urethritis. In a case of vaginitis and ophthalmia an autogenous antigen gave the same degree of reaction as did the stock antigen of three combined strains.

Cultures of the gonococcus from 24-hour blood agar transfers were planted on large tubes (2.5 cm. $\times$ 15 cm.) of slanted ascites agar and incubated for 24 hours. Care was taken that the seeding of the surface of the slants was uniform, and drying of the surface was prevented by cork stoppers in the tubes. The suspension obtained from six tubes was used in the preparation of 1 c.c. of the final product.

A somewhat more exact method of preparing the antigen was attempted by evaporating a suspension to dryness, and then taking up the weighed powdered residue in glycerin. This residue necessarily contained some soluble products from the culture medium, in addition to substances derived from the gonococcus. Serial dilutions of this extract were prepared, and the reactions obtained with them compared with the reactions from the extract prepared by the first method. It was found that an extract containing 0.1 gm. of the powdered residue in 1 c.c. of glycerin gave approximately the same degree of reaction as did the extract prepared by the first method. The reactions were progressively less, the greater the dilution of the gonococcin. A dilution of the extract containing 0.001 gm. per c.c. of glycerin gave a faint reaction in allergic individuals.

The time allowed for autolysis of the suspensions of the gonococcus seemed to affect the strength of the gonococcin. An antigen

prepared from a suspension of gonococci heated to 60° C. immediately after removal of the organisms from the surface of the culture medium did not give quite as strong reactions in gonococcal cases as did an antigen prepared from the same suspension and kept at 37° C. for 48 hours before heating to 60° C. In cases in which the cutaneous allergy was highly developed, the difference between the two antigens was absent.

A suspension of gonococci was evaporated to dryness, and the residue extracted for 48 hours with 95 per cent alcohol. An antigen prepared by evaporating the alcoholic extract and adding a suitable amount of glycerin gave only a slight reaction in allergic persons. The residue remaining after extraction by alcohol was extracted with water for 24 hours. An antigen prepared from this extract gave a good reaction in susceptible individuals.

METHOD OF INOCULATION.

The preparations of gonococcin and the control extract were kept in a battery of cork-stoppered vials. A separate needle was used for each preparation. When not in use, the needles were kept in vials of alcohol, each corresponding to a vial of antigen. In this way each needle was sterile, and used only for its own antigen.

Inoculations were made by gently rotating the point of the needle with a minute drop of antigen attached on the skin of the arm. Care was taken to avoid the puncture of capillaries. In all cases a series of at least three inoculations and one control was made, care being taken to make the inoculations as nearly uniform as possible.

THE CUTANEOUS REACTION.

The cutaneous reaction after the inoculation of gonococcin in infected individuals does not differ essentially from that following the inoculation of other antigens such as tuberculin. Within a few minutes small wheals may appear about the point of puncture of both antigen and control. After a few hours a papule is formed, with a surrounding area of hyperemia, and in 24 hours the maximum reaction is usually obtained. On the second day the hyperemia is less, and by the third day has usually disappeared. The papules remain for several days, and in pronounced reactions may

be visible seven to 10 days after inoculation. Delayed reactions have not been observed.

The control inoculation shows only a minute point at the site of trauma.

The degree of the reaction in gonococcal infections varies with the extent of the infection, and from time to time in the same case. Typical reactions in gonococcal arthritis or epididymitis show a papule 3 to 5 mm. in diameter, with a surrounding hyperemia of 7 to 10 mm. or more. Reactions of less degree were frequently observed in known gonococcal infections either early in the infection or later in the course of the disease.

Normal adults in whom previous gonococcal infection was excluded showed a lesion rarely more than 1-2 mm. in total diameter. Often the points of puncture showed nothing more than the control. Adults suffering from other diseases, such as typhoid fever, tuberculosis of bones and pleura, staphylococcus infections (furunculosis, osteomyelitis), leukemia, lobar pneumonia, etc., in whom previous gonococcal infection was excluded gave no more reaction than the average normal adult.

For the purposes of discussion the reactions obtained in this study have been classified as positive when over 5 mm. in total diameter, as negative when 3 mm. or less, and doubtful when the papule was small and the hyperemia indefinite or less than 5 mm. in diameter. This division, though arbitrary, is based on tests in a large number of normal and infected individuals, using antigens prepared in the manner indicated, and offers a convenient solution of the difficulty of discussing the differences in cutaneous reactivity of the cases studied.

In children in whom there is no history of gonococcal infection, about 50 per cent give no more reaction with gonococcin than with the control. In a number of the remainder a small area of hyperemia 2-3 mm. in diameter is obtained, and in a few, larger areas up to 5 mm., rarely 7 mm., are seen. This increased cutaneous sensitiveness in children has been observed in other infections, and has been explained by some on the ground that in children the amount of normal antibodies is proportionately larger than in adults. In children as in adults the increase in reactivity may be

observed in successive tests during the course of the infection, and a child whose skin gives a reaction of 1-2 mm. at the beginning of the disease, after two or three weeks, may give a pronounced reaction of 7-8 mm. The possible influence of infections of the nasal passages of these children by organisms, closely allied to the gonococcus, such as *M. catarrhalis*, must also be considered. The question of a group reaction will be discussed later.

Observations on patients with gonococcal infections soon demonstrated that while the degree of reaction may remain fairly constant from day to day, it is much more frequent for the reaction to vary in intensity from time to time.

The diameter in millimeters of the zone of hyperemia surrounding each papule was recorded 24 hours after inoculation. The results from three simultaneous inoculations were averaged, and this average used in plotting curves to show the fluctuations of the reaction in a given case. As a rule there was no marked difference between the three inoculations.

The daily inoculation of even minute quantities of the preparations may have produced a slight sensitization, but this was apparently very small compared to the much larger influence of the infection in the body.

In cases in which it was desired to study the development of immunity in infections unmodified by treatment, tests were made at intervals of three or four days.

The danger of confusion in the reactions through the production of antibodies by the albuminous constituents of the culture media was obviated by the use of the control inoculation.

The hyperemia resulting from the occasional infection of the point of inoculation of the antigen or control must be distinguished from a true reaction. Such infections usually show a minute white central area of pus formation. Careful preliminary cleansing of the skin with alcohol, and the making of multiple inoculations of each antigen will usually obviate this difficulty.

THE DEVELOPMENT OF CUTANEOUS ALLERGY.

Several cases of recent vaginitis in children in which the date of first discharge was known were tested at intervals of four to five

days. In all, the reaction in the first week was negative (i.e., there was no more reaction than occurs in normal individuals). In the second and third weeks, the papules became slightly larger, and by the fourth week pronounced papules with surrounding hyperemia were noted.

In epididymitis accompanying gonorrhea, the reaction varied in the cases studied. In several, tested on the third or fourth day of the epididymitis, cutaneous reaction was pronounced. In

CHART 1.—Cutaneous allergy with respect to gonococcal extracts in a man 20 years old; first attack of gonorrhea in September, 1910; recurrence in August, 1911; arthritis in October, 1911; no discharge at present; now suffers from tender heels and ankles, and recurrent hydrops of right wrist with 7 days' cycle. Injections of killed gonococci as shown on the chart.

two cases the reaction was faint on the second and third days, but by the fifth day, when the patient had begun to mend, the reaction became more definite.

In arthritis, the degree of the reaction varied greatly. In several cases of extensive arthritis, the reaction was negative or slight. Later, when improvement in general condition occurred, the cutaneous reaction became pronounced. In one case of extensive arthritis, in which improvement did not occur while under observation, a positive reaction was not obtained.

In infected individuals giving a weak cutaneous reaction, the reaction may become positive on a second test after the inoculation of gonococcus vaccine (Chart 1¹).

¹ The curves shown in these charts were constructed from successive determinations of the degree of cutaneous reaction following the inoculation of glycerin extracts of bacterial antigens. The degree of reaction was determined by recording the diameter in millimeters of the reactions obtained 24 hours after inoculation. In the gonococcal curves, each determination represents the average diameter of three simultaneous tests. The meningococcal curves were plotted from single determinations. Care was taken to make the inoculations as nearly as possible uniform in depth, and in the amount of antigen inoculated. The reactions obtained from day to day were measured, and the data recorded on slips of paper without

DURATION OF CUTANEOUS ALLERGY.

Several adults tested from one to two years after a single gonococcal infection gave positive reactions. A number of adults with a history of gonorrhea from 2 to 12 years previously gave

CHART 2.—Cutaneous allergy with respect to gonococcal extracts in a woman, 25 years old, who acquired gonorrhea one and one-half years ago; bilateral salpingitis. Panhysterectomy on April 3. Gonococci were found in wall of tube. Rapid recovery after operation.

reactions considerably more pronounced than the average normal adult with a definite negative history. Too much importance should not be attached to the results in this latter class of cases, as the possibility of a persistent gonococcal posterior urethritis or prostatitis was not excluded.

In arthritis the wave of immunity, as shown by cutaneous allergy, may rise and fall, even below the threshold of the cutaneous reaction, and it is probable that this oscillation occurs as well in other types of gonococcal infection.

A case of bilateral pyosalpinx (Chart 2) gave a positive reaction before operation, and after panhysterectomy the reaction remained at the same height till the patient passed out of observation three weeks later.

INFLUENCE OF OTHER INFECTIONS ON THE GONOCOCCIN REACTION.

Intercurrent diseases such as whooping cough, chicken-pox, and mumps, in children suffering from vaginitis, did not seem to

reference to previous figures, and later the accumulated results were plotted in curves. It is recognized that this method of recording results is open to criticism, particularly in the matter of small daily variations. The more pronounced variations, however, can hardly be attributed to errors in the methods of observation, and compare favorably in point of accuracy with the data obtained in laboratory experiments.

interfere with the gonococcal reaction. Three cases of gonococcal infection in persons with active syphilis gave unusually bright reactions.

TABLE 1.

	Reaction 5 mm. or More +	Reaction 3-4 mm. Indef- nite ?	Reaction No Reaction or 2-3 mm. —
Gonococcal arthritis.....	11	2	2
Epididymitis.....	6	1	1
Old gonorrhea 1-20 years.....	3	6	4
Ophthalmia.....	2	0	0
Iritis.....	2	0	0
Salpingitis.....	5	2	3
Vaginitis, Series I.....	9	0	2
Series II.....	13	9	4
Series III.....	7	3	8
Series IV.....	8	3	8
Normals and other diseases			
Gonorrhea denied. No signs.....	1	1	16
Puerperal sepsis clinically not gonorrheal.....	0	0	6
Fibroids—old, cystic ovaries, and endometritis.....	0	0	5
Children—other diseases { Series I.....	2	7	9
{ Series II.....	1	9	12

Table 1 shows the proportion of positive, negative, and doubtful reactions obtained in some of the series of gonococcal infections, using the arbitrary classification described above. The cases are arranged in groups, according to wards, clinics, and hospitals. In the series of arthritis, the diagnosis was established with certainty. The negative and doubtful reactions were met with for the most part in patients with extensive arthritis and little clinical evidence of recuperative power. Certain of these severe cases showed first a negative, and later a positive reaction when improvement had set in.

The several series of vaginitis show considerable variations in the proportions of positive and negative cases. This may be due in part to the fact that some series comprised cases of longer standing than others, and in part to the fact that although certain of these children were in vaginitis wards, suffering from vaginitis, the gonococcus could not be demonstrated in the smears or in cultures. It is of course recognized that a single culture from the vagina negative for the gonococcus, in the presence of many other organisms, is by no means conclusive evidence that the gonococcus is not present, but when such cultures are repeatedly negative for gonococcus, and show at the same time diplococcoid forms of other

persistently negative cutaneous reaction were studied by means of repeated vaginal cultures, and the gonococcus was not found. The same methods and media gave good growths of the gonococcus from other cases including vaginitis and urethritis. It seems likely; therefore, that in some cases of vaginitis in specific wards the gonococcus is not present.

In testing adults who were supposedly free from gonococcal infection, several were found, including a case of alcoholic cirrhosis, and one of tuberculous pleurisy, who gave rather marked cutaneous reactions. Two of these were women in whom an inactive infection could not be excluded. In the case of alcoholic cirrhosis, the habits of life of the patient were such that gonococcal infection was at least possible.

The finding of occasional positive reactions in supposedly non-gonococcal cases and the failure of some cases of arthritis to give continuously a positive reaction, suggest the advisability of further series of tests, before absolute reliance is placed on the reaction in diagnosis.

In salpingitis of varying duration (6 months to 10 years) about 50 per cent gave positive reactions. In the remainder a faint or negative reaction was obtained. This latter group contained several old cases in which the record of operation showed extensive adhesions, cystic tubes, and ovaries without active pus formation. In one of the cases giving a positive reaction, large pus tubes were found, from the walls of which the gonococcus was obtained (Chart 2).

CUTANEOUS ALLERGY IN MENINGOCOCCAL INFECTIONS.

Four cases of epidemic meningitis were studied. A boy of two years, convalescent in the fourth week after the onset of the infection by the meningococcus, gave a positive reaction to gonococcin. There was no sign or history of any gonococcal infection.

A youth of 19 in whom there was no history or evidence of gonococcal infection was tested on the second day of a moderately severe meningitis, and gave a negative reaction. Tests on the sixth and eighth days were likewise negative. Four doses of anti-meningococcic serum had been given on the second to the fifth days,

and the patient was afebrile and convalescent on the sixth day. On the 13th day, the gonococcin produced a reaction of 3 to 4 mm. and a glycerin extract of the meningococcus isolated from the patient produced a reaction of 6 mm. The allergy continued to increase, and on the 17th day a reaction of 5 mm. was obtained with gonococcin, and one of 10 mm. with the preparation of the meningococcus (Chart 6).

A third case of meningitis in a man of 30 years was much more severe. He received two doses of serum of 30 c.c. each on the second

CHART 6.—Cutaneous allergy with respect to meningococcal and gonococcal extracts in a case of epidemic meningitis. Antimeningococcic serum (30 c.c.) given by lumbar puncture on second, third, fourth, and fifth days of illness. Fine line=Temperature. Heavy broken line=Reaction to meningococcal extracts. Heavy solid line=Reaction to gonococcal extracts.

to fifth days, became afebrile for five days and then the symptoms returned with high fever, headache, etc. On the 13th day the reactions to preparations of the gonococcin and meningococcus were still faint, and remained so until the 19th day, when they began to increase (Chart 7).

A fourth case of epidemic meningitis in a man who gave no history or evidence of gonococcal infection showed slightly positive reactions to gonococcin on the 12th day of the disease.

Patients with gonococcal infection who showed a marked cutaneous allergy were tested with the same antigens as the meningococcal cases described above. Definite reactions were obtained in the gonococcal infections with inoculations of a preparation of the meningococcus, though here the reaction was less than that obtained with the gonococcin.

GROUP REACTIONS.

These reactions with the gonococcus and meningococcus form a further demonstration of the close relationship which already has been shown by many workers by comparisons of the cultural characteristics of the two organisms, and by studies of their agglutinins and precipitins. It is possible that the micrococcus catarrhalis may be included in this group reaction, and infection by this organism may explain the occurrence of certain doubtful gonococcal reactions observed in persons supposedly free from gonococcal infection.

CHART 7.—Cutaneous allergy with respect to meningococcal and gonococcal extracts in a case of epidemic meningitis showing recrudescence of the disease on the 12th day and again on the 24th day, as shown by the temperature curve. Antimeningococcal serum given by lumbar puncture as indicated on the chart. The cutaneous allergy developed slowly and to a relatively slight degree. Fine line = Temperature. Heavy broken line = Reaction to meningococcal extracts. Heavy solid line = Reaction to gonococcal extracts.

Similar group reactions have been noted in studies of the inter-reactions of tuberculin and leprolin, and in the tricothylin reaction in which antigens prepared from tricothyton, microsporon, and achorion will all give reactions in persons infected with tricothyton, and the tricothylin will give reactions in persons suffering from favus.

EXPERIMENTAL ALLERGY IN MAN AND ANIMALS.

A man suffering from a fracture of the leg, in whom previous gonococcal infection was excluded by careful inquiry into the history and by examination, was found to give a negative cutaneous reaction to gonococcal. He was then given repeated subcutaneous injections of gonococcus vaccine and the subsequent cutaneous

reactions recorded (Chart 8). The maximum reactions were by no means as large as those often seen in infected persons, but compared to the reaction before inoculation, they showed a definite increase in cutaneous reactivity following the injections.

A large rabbit was given seven intraperitoneal injections of suspensions of gonococci grown on rabbit's blood agar. Five weeks after the last injection cutaneous tests were made with antigen and control. Slight papules developed after 24 hours at the site of inoculation of the antigens. The control inoculation showed no reaction. This test was repeated with the same result. A suspension from one blood agar tube of the same strain of gonococcus

CHART 8.—Cutaneous allergy with respect to gonococcal extracts in a man without gonococcal infection but injected with killed gonococci as shown in chart.

was injected intravenously. A cutaneous test on this date gave papules 2 to 3 mm. in diameter. Two days later a reaction of 5 mm. with a definite hyperemia was obtained. Subsequent tests gave less marked reactions.

PASSIVE ALLERGY IN ANIMALS.

A number of normal guinea-pigs (250 gms.) and rabbits were shaved and cutaneous tests made. In all animals tested, no reaction beyond that due to trauma was obtained either with antigen or control.

Four of the pigs were then given intraperitoneal injections of 1 c.c. of commercial antigonococcus serum. Cutaneous tests after 24 and 48 hours were negative.

Two pigs were given 5 c.c. of serum intraperitoneally. Tests

made daily for the succeeding four days showed nothing beyond an occasional indefinite papule.

A pig was given 5 c.c. of concentrated antigenococcus serum. On the following day the cutaneous test was entirely negative, but on the second day a papule of 3 mm. was obtained, while the control was negative. On the third and fourth days the reaction was negative.

A half-grown rabbit was given 5 c.c. concentrated¹ antigenococcus serum intravenously. Slight papules appeared after cutaneous inoculation on the second, third and fourth days.

A rabbit was given 13 c.c. of fluid aspirated from the knee of a patient with gonococcal arthritis. Repeated tests on subsequent days were negative.

In these and similar experiments, the cutaneous reactivity was apparently slightly increased after the larger doses of concentrated serum, but the results were by no means marked.

SUMMARY.

The cutaneous inoculation of glycerin extracts of autolyzed gonococci in patients infected by the gonococcus produces a well defined reaction. This reaction is not usually obtained in normal persons, nor in those suffering from other infectious diseases.

In persons recently infected, the reaction is negative and increases gradually during the course of the disease.

In the more chronic forms of gonococcal infection, such as arthritis, the degree of the cutaneous reactivity varies from day to day, and these variations may be correlated with the changes in the clinical course of the disease.

Cases of severe infection, such as extensive arthritis, may give negative reactions. Later, when improvement has occurred, the reaction becomes positive.

In general, a positive reaction is obtained in patients with gonococcal infection at some time during the course of the disease.

In normal persons the gonococcin prepared in the manner

¹ Commercial antigenococcus serum was concentrated by Dr. P. G. Heinemann. The antibody content of the concentrated serum was estimated by Dr. Gatewood as about four times that of the original serum. *Jour. Infect. Dis.*, 1912, 10, p. 416.

described gives a cutaneous reaction rarely more than 2 to 3 mm. in diameter.

Occasionally in adults and somewhat more frequently in children fairly marked reactions are met with where previous gonococcal infection can be excluded. In these cases the normal antibodies may be increased to an unusual degree. It is possible that normal individuals may be found who will give reactions to antigens prepared from many pathogenic organisms. The possibility must also be borne in mind that infection by one organism may give rise to an increase in the proteolytic power of the serum for other organisms.

The cutaneous reactions obtained with meningococcal and gonococcal antigens suggest that we are dealing with a group reaction.

In diagnosis, a positive reaction is to be regarded as confirmatory evidence of gonococcal infection. Other infections, such as those by the meningococcus or *M. catarrhalis*, which may give rise to a group reaction, must be excluded. The clinical value of the reaction must be determined by further tests, and its limitations defined by a study of many groups of cases.