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Oscar C. Hansen-Pruss, … , Warfield T. Longcope, D. P. O'Brien

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Research Article

SKIN REACTIONS TO FILTRATES OF HAEMOLYTIC STREPTOCOCCI IN ACUTE AND SUBACUTE NEPHRITIS[1]

By OSCAR C. HANSEN-PRUSS, WARFIELD T. LONGCOPE, AND D. P. O'BRIEN[2]

(From the Medical Clinic, the School of Medicine, Johns Hopkins University, Baltimore)

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In a previous communication (1) it was noted that haemolytic streptococci isolated from the tonsils, adenoids or accessory nasal sinuses of cases of acute and subacute glomerular nephritis produced, in broth cultures, "toxins" which caused skin reactions similar to those caused by the "Dick Toxin." While studying the property of these filtrates, it was observed that intense skin reactions often occurred in patients suffering from acute and subacute nephritis associated with infections caused by haemolytic streptococci. A systematic study was, therefore, made of the incidence and intensity of the skin reactions to these bouillon filtrates of haemolytic streptococci in three groups of cases; first, patients suffering from acute and subacute nephritis; secondly, normal individuals and patients affected with miscellaneous conditions, and thirdly, patients suffering from uncomplicated acute tonsillitis. There will be no attempt to discuss at this time the nature of these filtrates.

It is, however, to be noted that many observers have found that haemolytic streptococci recovered from various forms of infection are capable of elaborating "toxic" substances when grown in broth (2, 3, 4, 5, 6, 7, 8, 9, 10, 11).

Although these filtrates are usually more resistant to heat and less potent than the "Dick Toxin," yet they possess other properties in common with the "Dick Toxin," for they are frequently neutralizable by antiscarlatinal serum (3, 7, 9, 10) and are considered by some to differ only quantitatively from the "Dick Toxin," though qualitative differences have also been observed (10, 11, 13, 13a).

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[2] Jacques Loeb Fellow in Medicine.

The significance of the Dick reaction and of the reactions caused by filtrates obtained from the growth of non-scarlatinal strains of haemolytic streptococci is not perfectly clear. Mackenzie and Hanger (5) considered that the reactions which they obtained indicated an acquired allergy, and that the skin reaction was probably similar in nature to the local tuberculin reaction. There is increasing evidence to sustain this point of view. Dochez and Sherman (12) have shown that the skin of rabbits and guinea pigs, previously inoculated with living cultures of *Streptococcus scarlatinae,* becomes sensitive to filtrates of this organism; while Zinsser and Grinnell (13) have observed that the pronounced skin reactions to haemolytic streptococcus filtrates and to the "Dick Toxin," which can be obtained in guinea pigs infected with haemolytic streptococci, may fade or disappear after the infection has persisted for some days, and later reappear again. They conclude that these reactions are allergic in nature and comparable to the tuberculin reaction. We have observed the same phenomena in rabbits infected subcutaneously by strains of haemolytic straptococci obtained from infections in acute nephritis. The skin of the rabbit which, under normal conditions gives no reaction to the intracutaneous injection of 0.2 cc. of undiluted filtrate, may react to the same filtrates within five to seven days after the onset of an induced local streptococcus infection, by an area of erythema and oedema 1–2 cm. in diameter. Two or three weeks later the hypersensitiveness of the skin usually disappears. We could not determine that these reactions were specific for different strains. Infection of the rabbit by one strain of haemolytic streptococcus rendered the skin sensitive to filtrates from many strains of haemolytic streptococci as well as to the "Dick Toxin." Dochez and Stevens (14) have shown that two phases of cutaneous allergy develop when rabbits are immunized with filtrates of haemolytic streptococci from erysipelas. The reactions occurring during the first period of allergy can be neutralized with erysipelas immune serum, but the reaction during the second phase cannot.

The important observations of Cooke (15), upon the nature of the Dick reaction, bring strong evidence to show that the Dick reaction depends upon an allergy acquired, through streptococcus infections, during early life. A positive reaction may become temporarily

negative through desensitization or be rendered permanently negative by the production in the body of antitoxin. Kirchner (16) states that he can sensitize the cornea of rabbits against filtrates of both scarlatinal strains and non-scarlatinal strains of haemolytic streptococci.

METHODS

In the present investigation 18 strains of hemolytic streptococci were employed. Thirteen of them were of the beta type and five of alpha type. The organisms were grown in beef infusion peptone broth of pH 7.4 for 18 hours at 36.5°C., which was then filtered through Berkefelt candles and Seitz filters. For skin reactions the filtrates were usually employed in 1–100 dilutions. When positive skin reactions were obtained with these dilutions, tests were made as a rule with 1–500, 1–1000, 1–2000 and occasionally 1–5000 dilutions. For each test 0.1 cc. of the dilution was employed. Stock bouillon in 1–100 dilution was employed as a control and a Dick reaction with 1 S.T.D. of "toxin" was always made at the same time. The skin reactions were read at the end of 18 hours and 24 hours. The reaction was considered negative unless the area of erythema measured more than 1.0 cm. in one diameter. Reactions of 1 to 1.5 cm. were termed +; reactions of 1.5 to 2.0 cm. were termed ++, reactions of 2.0 to 2.5 cm. in diameter were termed +++ and all reactions 2.5 cm. in diameter or over were designated ++++.

Since the observations have been carried on over several years it has been necessary to prepare many batches of filtrates. These have been titrated against a known reactor before they were employed for tests. It was surprising to note with what regularity a single strain produced a filtrate of approximately the same strength.

Skin reactions in normal persons and patients suffering from miscellaneous conditions.

Mackenzie and Hanger (5) found young children quite regularly insensitive to the filtrates which they employed, but obtained positive reactions in a very large proportion of adults. They were not able to correlate these reactions with previous or existing infections, nor could they find any apparent relation between the presence of these skin reactions and any one disease or group of diseases. They employed comparatively large doses of filtrate using 0.03 to 0.04 cc. of undiluted broth filtrates. Howell and Corrigan (17) found that a high percentage of persons, both healthy and diseased, reacted positively to streptococcus filtrates, and that there was no apparent correlation between the skin reactions and the etiological factors of the

disease. Children that were susceptible to streptococcus infections gave a higher percentage of positive reactions with all streptococcus filtrates than did other children or adults. They suggest that a positive skin reaction with streptococcus filtrates may indicate susceptibility to streptococcus infections. Lash and Kaplan (2) obtained 8.1 per cent positive skin reactions in 247 women who were either normal (20), pregnant (86), or puerperal (141), with filtrates in 1–1000 dilution of a streptococcus obtained from a case of puerperal septicaemia. Birkhaug (6) found that 21 per cent of school children, between the ages of 7 and 17 years, gave positive skin reactions to the toxin from *Streptococcus erysipelatis*, while 27 per cent of 135 hospital patients, between the ages of 17 and 72 years, gave positive reactions to 1 S.T.D.

Amoss, Hansen-Prüss and Bliss (18) state that 70 per cent of normal men, and 80 per cent of normal women give more or less marked skin reactions to erysipelas toxin in 1–100 dilution.

Statistics concerning the occurrence of positive Dick reactions in children and adults vary considerably. Dick and Dick (19) give 58.8 per cent of positive reactions in 1250 persons; Lees (20) 49.8 per cent positive reactions amongst 530 University students; Zingher (21) 26.3 per cent positive reactions amongst children in New York City while Dyer (22) found that school children from rural and urban districts might show a variation in positive reactions from 100 per cent to 25 per cent.

It is obviously impossible to make accurate comparisons of the incidence of positive skin reactions to streptococcus filtrates obtained by different observers. So much depends upon the dosage, the strength of the various filtrates and the group of individuals tested. It is possible, however, to compare with a considerable degree of accuracy the tests performed with standardized filtrates by a single observer in different groups of patients.

We have tested the skin of 60 individuals, who were supposedly normal or who were suffering from a miscellany of conditions, with bouillon filtrates of the strains of haemolytic streptococci isolated from infections in acute nephritis. Eighteen different strains were employed in the preparation of these filtrates, and the filtrates from 2 to 16 strains were employed for tests on each individual. An average

of 9 filtrates was used for tests in each person. Most of these persons were between 18 and 35 years of age. Of the 60 individuals one-half were supposedly normal, the other half, though not acutely ill, were affected with a variety of conditions, such as chronic valvular heart disease, duodenal ulcer, multiple sclerosis, hyperthyroidism, chronic tonsillitis, diabetes, hereditary telangiectasis, chronic sinusitis,

TABLE 1

Incidence of reactions. Normals

	Total number	+ or more		++++		Dick +	
		Number	Per cent	Number	Per cent	Number	Per cent
Subjects	60	38	62.2	15	25	14	20.3
Tests	542	167	30.8	33	6		

TABLE 2

Reactions with less dilute filtrates. Normals

Subject	Strain of filtrate	Intensity of reaction at following dilutions of filtrate		
		1-100	1-50	1-20
1	a	0	+++	
	b	++	++++	
2	a		0	0
	b		0	0
3	a	0	0	
	b	+	++++	
	c	0	+++	
4	a	0	+	++
	b	0	0	+
	c	0	0	
	d	+	+	+++

arteriosclerosis, chronic tuberculosis, convalescence from pneumonia and typhoid fever.

Table 1 gives the incidences of total reactions, the incidence of strong reactions and the proportions of positive reactions in this group of control cases.

It was found that about two-thirds of all these patients gave some

reaction to one or more of the filtrates in 1–100 dilutions, but that only one-fourth of the patients gave strong reactions in this dilution. Comparatively few patients gave reactions to dilutions of 1–500 or more. Of 33 individuals, selected largely from those who had reacted to the filtrates in 1–100 dilutions, who were tested with a 1–500 dilution of the filtrates 15 or 45.4 per cent gave + or greater reactions, while only 3 or 9 per cent gave ++++ reactions.

Four of the entire number of the negative reactors were tested with less dilute filtrates, 1–50 and 1–20 being employed. Two individuals who gave negative reactions with 1–100 dilutions showed +++ reactions with 1–50 dilutions. One individual gave a negative reaction at 1–50 but a + reaction at 1–20, and one individual gave negative reactions both with 1–50 and 1–20 dilutions. The titrations of these reactions are given in Table 2.

The positive Dick reactions were obtained almost entirely among the individuals that gave positive reactions to the bouillon filtrates. Of the 14 positive Dick reactions 13 occurred amongst the positive reactors and one amongst the negative reactors

It is important to draw attention to the fact, that, in the miscellaneous group, there were five individuals who suffered from chronic sinusitis or chronic tonsillitis. All five of these patients gave positive reactions and four of them showed ++++ reactions to one or more of the filtrates. Furthermore all of these five individuals came in the group of 15 who gave + reactions in 1–500 dilutions, while the 3 individuals who gave ++++ reactions in 1–500 dilutions belong to this group of chronic tonsillitis and sinusitis.

From the observations made on these 60 persons, it may be concluded that the skin reactions to these bouillon filtrates of haemolytic streptococci vary considerably in different individuals. The skin of some individuals may be almost insensitive to comparatively large doses of the filtrates, while the skin of other persons may react quite vigorously to considerably diluted filtrate. It was also observed that reactions to the same filtrates might vary from time to time. In several individuals reactions that were at first ++ to ++++ became on subsequent tests +. It was also noted that in this control group the individuals having obvious chronic tonsillitis or sinusitis were among those most likely to give strong reactions.

Skin reactions in acute and subacute nephritis

The results obtained from the skin tests made upon patients suffering with acute and subacute nephritis differed, in several respects, from those in the control groups.

Twenty-seven patients were tested. An average of 9 filtrates from different strains was used in each patient. Table 3 shows the number and percentage of positive reactions obtained in these twenty-seven patients with 0.1 cc. of 1–100 dilutions of filtrates.

It may be seen from the table that this group of patients suffering from nephritis gave reactions much more frequently than the control groups; that they gave many more ++++ reactions, and that they reacted to a greater number of filtrates. When one measures the susceptibility of these patients to the streptococcus filtrates, by titrating the dose of filtrate, the difference becomes even more striking. Of 12 patients tested with 1–500 dilutions 9, or 75 per cent gave + to ++++ reactions, whereas in the control group only 45.4 per cent of 33 cases tested with 1–500 dilutions gave + reactions. Of the 12 nephritics 6, or 50 per cent, gave ++++ reactions with 1–500 dilutions whereas only 9 per cent of the controls gave ++++ reactions with this dilution. In the cases of nephritis, many positive reactions were obtained with still greater dilution, of filtrate. Of 7 patients tested with 1–1000 dilution, 5 gave + reactions or greater and 2 ++++ reactions. Of 5 patients tested with 1–2000 dilutions, 2 gave ++++ reactions, and one of two patients tested with 1–5000 dilutions gave a + reaction.

TABLE 3

Incidence of reactions. Nephritis

	Total number	+ or more		++++		Dick +	
		Number	Per cent	Number	Per cent	Number	Per cent
Patients	27	22	81.4	18	66.6	9	33.3
Tests	259	162	62.5	62	23.9		

In the group of nephritics, there seemed to be no definite relationship between reactions from filtrates and reactions from "Dick Toxin." There were 9 of the 27 patients who gave positive Dick reactions. All

of these gave ++++ reactions with the bouillon filtrates. Of the 18 patients who gave negative Dick reactions 9 or 50 per cent gave ++++ reactions with the bouillon filtrates. It can only be said, therefore, that when the Dick reaction was positive the reactions with filtrate were strongly positive, but that strongly positive reactions with filtrates occurred in one-half the patients that gave negative Dick reactions.

Amongst the 27 nephritics, there were 4 cases that gave no reactions to any filtrates of the streptococci, and that also gave negative Dick reactions. Three of these patients had marked oedema at the time the tests were made. One of these three, who had much oedema at the time the first tests were made, was retested later after the oedema had subsided and still showed completely negative reactions. The fourth had only moderate oedema. It is possible that marked oedema of the subcutaneous tissues may favor rapid absorbtion of the injected bacterial filtrate, such as occurs with sodium chloride solution, and thereby reduce the liability of a reaction in the skin, though it is more probable that the skin of these patients was actually insensitive to the filtrates.

The skin reactions in this group of 27 nephritics seemed to persist in the same degree and intensity in many patients for months or even years. Two patients have shown skin reactions of the same intensity for 8 months, 2 for 1 year, 1 for 1 year and 8 months, one for 2 years, 2 for 2 years and 8 months, and one for 3 years. Among this group of 9 retested patients, there are three who have, apparently, recovered completely from their attacks of acute nephritis as well as from the infection. The acute nephritis in each instance was associated with an acute tonsillitis due to β haemolytic streptococci. In all three, tonsillectomy was performed during the early stage of nephritis. Repeated examinations over a period of 8 months in one case and 2 years and 8 months in the other two have shown that they were free from infection, and cultures from the pharynx and nasopharynx have not shown β haemolytic streptococci. Three of the 9 patients retested are symptomatically well, but still show traces of albumen and occasional hyaline casts in the urine, while cultures from the pharynx have shown from time to time haemolytic streptococci; in the remaining group of three of the total 9 cases, the original acute or subacute

nephritis has become chronic, infections have persisted and cultures from the infections of the pharynx and paranasal sinuses have shown constantly haemolytic streptococci.

These observations indicate that the increased sensitiveness of the skin of patients, suffering from acute and subacute nephritis, may persist for long periods of time, and that skin reactions of great intensity, in these patients, are not necessarily dependent upon the existence of a demonstrable infection or upon the carrier state.

It seemed necessary, however, to obtain further information as to the relation of the positive skin reaction to acute infections, produced by haemolytic streptococci of β type, occurring in patients in whom there was no evidence of a complicating acute nephritis. For this purpose, cases of uncomplicated acute tonsillitis were selected. Skin

TABLE 4

Incidence of reactions. Tonsillitis

	Total number	+ or more		++++		Dick +	
		Number	Per cent	Number	Per cent	Number	Per cent
Subjects	22	21	95.4	4	18.1	11	50
Tests	123	70	56.9	4	3.2		

reactions were performed with the bouillon filtrates in 22 such cases. Haemolytic streptococci were obtained in cultures from the tonsils in all cases. An average of five filtrates was employed for the tests in each case. In all but four, the filtrates were used in 1–500 dilutions, and therefore the results are not exactly comparable to those obtained in the control groups. The table 4, however, shows the incidence of positive reactions in this group of uncomplicated tonsillitis.

It will be seen that though a very large percentage of these cases gave positive reactions, a comparatively small number showed strongly positive reactions in 1–500 dilution; in the tonsillitis group 18.1 per cent and in the nephritis group 50 per cent. Though the total number of cases is small, the pronounced variations are indicative of considerable difference in the sensitiveness of the three groups to the bouillon filtrates.

DISCUSSION

A study of the skin tests made with filtrates of broth cultures of haemolytic streptococci, in these three groups of cases, shows the necessity, in any comparative investigation, of using different dilutions of the filtrate to distinguish varying degrees of reactivity of the skin. Amongst the individuals in the three groups, one finds, by titrating the reaction, all transitions from those, who are practically insensitive to the filtrates in the doses employed, to those who react vigorously to 1–2000 dilutions. The control group includes the largest proportion of poor reactors, whereas the nephritic group contains the largest number of strong reactors. The tonsillitis group contains many reactors, but comparatively few strong reactors. Table 5 demonstrates quite clearly these differences.

TABLE 5

Summary of incidence of reactions

	Diagnosis	Total number	+		++++	
			Number	Per cent	Number	Per cent
Cases	Controls	60	38	62.2	15	25
	Tonsillitis	22	21	95.4	4	18.1
	Nephritis	27	22	81.4	18	66.6
Tests	Normal	542	167	30.8	33	6.0
	Tonsillitis	123	70	56.9	4	3.2
	Nephritis	259	162	62.5	62	23.9

In the nephritic group, not only was the proportion of strongly positive reactions very high, but each positive reactor in the group showed strongly positive reactions to many more strains than the positive reactors in the other groups. Though the total number of cases is not large, yet the differences are so pronounced between the groups, that one is inclined to attribute them to actual variations in the susceptibility to the filtrates rather than to chance. The results obtained, both in the control group and in the tonsillitis group, indicate that persons suffering from various forms of infection due, to β haemolytic streptococci, are somewhat more likely to give positive skin reactions to these streptococcus filtrates than are normal individuals. It does not seem, however, that this propensity can account entirely for

the preponderance of strongly positive skin reactions in the nephritic group; for the nephritics continued to show this peculiarity, in several instances, for months or years after the streptococcus infection had disappeared. Moreover, if one regards the results from another point of view, it appears that a fair proportion of all the individuals who gave strongly positive skin reactions were nephritic. Of the total number of 109 individuals tested, 37 or 33.9 per cent gave strongly positive reactions, and of these 37 strongly positive reactors, 18 or 48.6 per cent were nephritic.

There appears, actually, to be a quantitative difference in the skin reactions to these filtrates, between many patients with nephritis and the average normal individual, or the patient suffering from an uncomplicated acute streptococcus tonsillitis. This difference consists in a heightened susceptibility of the skin to the culture filtrates of haemolytic streptococci. It seems possible, that there may be some connection between the heightened susceptibility of the skin to these filtrates, and the occurrence of acute glomerular nephritis as a complication of local streptococcus infection. It is becoming more and more obvious that in the streptococcus infections, as in tuberculosis and syphilis, an induced allergy, towards the protein of the streptococcus or to the products of its growth, accounts for some of the variations in the form of the infection and of its complications. Bristol (23) has expressed the view that the exanthem of scarlet fever is an allergic reaction to the local streptococcus infection, and has reviewed the literature on this subject. The more recent investigations by Dochez and Stevens (14) and by Cooke (15) go far to substantiate this idea. Dochez and Stevens conclude that both the Dick reaction and the rash in scarlet fever are dependent upon previous sensitization of the individual to haemolytic streptococci, and are to be looked upon as allergic reactions of the individual to products of *Streptococcus scarlatinae*. Cooke adds considerable evidence to confirm this hypothesis in which he thoroughly concurs.

Another streptococcus infection, which presents certain features that have been interpreted as allergic in nature, is erysipelas. Amoss, Hansen-Prüss and Bliss (18) bring evidence to show that recurrent attacks of erysipelas are allergic in character, and find that the skin reactions to bouillon filtrates of erysipelas strains of haemolytic

streptococci are pronounced in all patients suffering from recurrent attacks of erysipelas. Birkhaug (24) has expressed a similar view; while Francis (25) concludes, from a study of erysipelas, that allergy plays an important rôle both in the pathogenesis of the disease and in recovery from the local lesion.

Some observations have likewise been made upon the allergic reactions to non-haemolytic streptococci. The work of Birkhaug (26), Kaiser (27) and Swift, Wilson and Todd (28) indicates that skin reactions to various strains of non-haemolytic streptococci, or to their filtrates, are more frequent in rheumatic fever than in non-rheumatic patients; while Swift, Wilson and Todd observed a larger proportion of positive skin reactions, during the active stage of the disease, than during the latent period. Swift, Hitchcock and Derick (29), moreover, have obtained general tuberculin like reactions, occasionally with reactivation of quiescent rheumatic foci, in patients with rheumatic fever who have been injected intravenously with heated killed vaccines of both green and haemolytic streptococci, or with nucleo protein of haemolytic streptococci. Swift (30), in particular, has done much to further the conception that the arthritis of rheumatic fever is an allergic reaction, the result of preliminary sensitization of the joints to non-haemolytic streptococci; and Zinsser (31) is inclined to accept this hypothesis.

The idea that the inception of acute glomerular nephritis may be dependent upon an allergic reaction of the kidneys is not new, for both Schick (32) and von Pirquet (33) suggested, many years ago, that the acute nephritis of scarlet fever might be interpreted as an allergic manifestation of this disease. An attempt was made by one of us, some time ago, to produce nephritis in animals by repeated anaphylactic shock; (34) and though these experiments, performed with soluble proteins, did result in degenerative lesions in the epithelium of the kidney tubules, with inflammatory reactions occasionally affecting the glomeruli, the pathological picture of diffuse glomerular nephritis was not obtained, and the results do not seem applicable to an explanation of the origin of nephritis in human beings. It seems possible, however, that when the body has become sensitized to an infection, the kidney may respond, in somewhat the same manner as the skin, when the products of bacterial growth are brought in direct contact with the

kidney cells. Long and Finner (35) have recently described the typical lesions of diffuse glomerular nephritis produced, in the tuberculous pig, by the injection of tuberculin into the renal artery.

If the heightened skin reaction to the filtrates of haemolytic streptococci can be interpreted as allergic reactions, then our observations indicate, that many patients, suffering from acute and subacute nephritis, are quite highly allergic to some constituent of haemolytic streptococci or to substances elaborated by these organisms. Continued investigations upon the incidence of haemolytic streptococcus infection, at the onset, during the course and with exacerbations of acute and subacute glomerular nephritis, have confirmed us in the view that this relationship is too frequent and too close to be purely incidental. Repeated cultures from the urine, even during the early stages of acute nephritis, have not shown haemolytic streptococci, except in the rare instances of what is probably a focal form of glomerular nephritis; and we have not obtained any evidence to show that the diffuse glomerular nephritis is the result of an actual infection of the kidney by bacteria. Though the idea, so frequently suggested, that the diffuse glomerular lesions are produced by the direct action of a true toxin cannot be dismissed, it seems much more probable that the reaction in the kidney may be allergic in nature, similar possibly to the reaction in the skin, and dependent upon a sensitization of the kidney cells to the haemolytic streptococci or the products of their growth.

If such a condition existed, one would scarcely expect absolute correlation between the skin reaction and the kidney reaction, for in other forms of sensitization this does not occur. Most patients suffering from allergic hay fever give skin reactions to the substances causing the hay fever or asthma, but they may, in addition, give skin reactions to many substances that are not concerned in the production of their asthma or hay fever. Conversely, the ingestion of a particular kind of food may cause urticaria and gastro-intestinal symptoms in patients whose skins do not react to extracts of this especial food. The correlation, therefore, between the skin reaction and the somatic reaction is not absolutely constant. Should the same conditions hold for streptococcus infections, it would not be surprising to encounter patients who gave strong skin reactions to filtrates of haemolytic streptococci, and yet did not develop nephritis during the course of a

streptococcus infection; and, on the other hand, observe occasional instances in which nephritis occurred, during the course of a streptococcus infection, in an individual who did not show exaggerated skin reactions to the filtrate.

In the groups of patients which we have studied, however, the most intense and the most numerous skin reactions to filtrates of haemolytic streptococci have occurred in those suffering from acute and subacute nephritis. Though the nephritis occurred, in the majority of instances, in persons suffering from infections caused by haemolytic streptococci, the positive skin reactions themselves, it was found, might persist long after the disappearance of the infection, and when the patient had apparently recovered from nephritis. It was, moreover, found that almost one half of the strongly positive reactors were nephritic.

SUMMARY

Skin reactions to the filtrates of haemolytic streptococci were studied in three groups of cases: (1) A control group of normal individuals and patients suffering with a variety of diseases, (2) patients with acute tonsillitis, (3) patients with acute and subacute nephritis.

In the control group 62 per cent were found to give positive skin reactions, but only 25 per cent strongly positive reactions; in the tonsillitis group 95.4 per cent were found to give positive skin reactions, but only 18.1 per cent strongly positive reactions; in the nephritis group, however, 81.4 per cent gave positive skin reactions, and 66.6 per cent strongly positive reactions.

The positive skin reaction is regarded as an evidence of allergy to the haemolytic streptococcus or the products of its growth.

The preponderance of strongly positive reactions in the nephritis group indicates that these patients may be highly allergic to the haemolytic streptococcus or the products of its growth.

It is suggested that the development of acute diffuse glomerular nephritis, in patients suffering from haemolytic streptococcus infections, may be referable to the products of the growth of the haemolytic streptococcus acting upon previously sensitized kidney cells.

BIBLIOGRAPHY

1. Longcope, W. T., O'Brien, D. P., McGuire, J., Hansen, O. C., and Denny, E. R., J. Clin. Invest., 1927, v. 7. Relationship of Acute Infections to Glomerular Nephritis.
2. Lash, A. F., and Kaplan, B., J. Am. Med. Assoc., 1925, lxxxiv, 1991; 1926, lxxxvi, 1197; 1427. Puerperal Fever.
3. Kirkbride, M. B., and Wheeler, M. W., J. Immunol., 1926, xi, 477; 1927, xiii, 19. Studies of the Toxins of the Hemolytic Streptococci Associated with Scarlet Fever.
4. Teichmann, J., Ztschr. f. Immunitätsfrsch., 1926, xlviii, 466. Experimentelle Prüfung des Dick-Toxins.
5. Mackenzie, G. M., and Hanger, F. M., Jr., J. of Immunol., 1927, xiii, 41. Allergic Reactions to Streptococcus Antigens.
6. Birkhaug, K. E., Proc. Soc. Exp. Biol. and Med., 1925, xxiii, 201, 291. Studies on the Biology of the *Streptococcus erysipelatis*. IV. Toxin Production of the *Streptococcus erysipelatis*.
7. Smith, J., J. Path. and Bact., 1927, xxx, 651. The Exotoxins of the Haemolytic Streptococci.
8. Okell, C. C., and Parish, H. J., Lancet, 1928, i, 748. The Relationship of Scarlet Fever to Other Streptococcal Infections.
9. Zlatogoroff, S. I., and Derkatch, W. S., J. Infect. Dis., 1928, xlii, 56. On the Specificity of Scarlet Fever Streptococci.
10. Ando, K., Kurauchi, K., and Ozaki, K., J. Immunol., 1928, xv, 191; 217. Studies on the "Toxins" of Hemolytic Streptococci. I. Relationship of the Toxins of Different Hemolytic Streptococci as Brought Out by Tests on the Human Subjects.
11. Hirszfeld, H., Mayzner, M., and Przesmycki, F., Ztschr. f. Immunitätsfsch., 1928, lvii, 414. Untersuchungen über Streptokokkengifte.
12. Dochez, A. R., and Sherman, L., Proc. Soc. Exp. Biol. and Med., 1925, xxii, 282. Some Reactions in Sensitized Guinea Pigs to the Filtrate of Scarlatinal Streptococcus.
13. Zinsser, H., and Grinnell, F. B., J. Immunol., 1925, x, 725. Further Studies on Bacterial Allergy. Allergic Reactions to the Hemolytic Streptococcus.
13a. Williams, A. W., Am. J. Pub. Health, 1925, xv, 129. The Relationship Between Different Antibodies.
14. Dochez, A. R., and Stevens, F. A., J. Exp. Med., 1927, xlvi, 487. Studies on the Biology of Streptococcus. VII. Allergic Reactions with Strains from Erysipelas.
15. Cooke, J. V., Am. J. Dis. Child., 1927, xxxiv, 969; 1928, xxxv, 762, 772, 781, 784, 974, 983, 991. Scarlet Fever.
16. Kirchner, O., Ztschr. f. Immunitätsfsch., 1928, lv, 157. Versuche über die Wirkung der Filtrate von Scharlach-streptokokken und anderen Streptokokken auf die Kaninchenkornea.

17. Howell, K. M., and Corrigan, M., J. Infect. Dis., 1928, xlii, 149. Skin Reactions with Bacterial Filtrates of Anhemolytic Streptococcus, Hemolytic Streptococcus and *B. typhosus*.
18. Amoss, H. L., Hansen-Prüss, O. C., and Bliss, E. A., Trans. Assoc. Am. Phys., 1928, xliii, 259. Erysipeloid Reactions as an Allergic Response.
19. Dick, G. F., and Dick, G. H., J. Am. Med. Assoc., 1925, lxxxiv, 1477. Results with the Skin Test for Susceptibility to Scarlet Fever.
20. Lees, H. D., J. Am. Med. Assoc., 1927, lxxxviii, 1133. The Dick Test with Active and Passive Immunization for Scarlet Fever.
21. Zingher, A., J. Am. Med. Assoc., 1924, lxxxiii, 432. The Dick Test in Normal Person and in Acute and Convalescing Cases of Scarlet Fever.
22. Dyer, R. E., Caton, W. P., and Sockrider, B. T., Public Health Reports, 1926, xli, 1159. Results of Dick Tests Made on Different Groups.
23. Bristol, L. D., Am. J. Med. Sci., 1923, clxvi, 853. Scarlet Fever as a Reaction of Hypersensitiveness to Streptococcus Protein.
24. Birkhaug, K. E., J. Am. Med. Assoc., 1928, xc, 1997. Erysipelas. VIII. Bacterial Allergy to *Streptococcus erysipelatis* in Recurrent Erysipelas.
25. Francis, T., Jr. J. Clin. Invest., 1928, vi, 221. Studies on Pathogenesis and Recovery in Erysipelas.
26. Birkhaug, K. E., J. Infect. Dis., 1927, xl, 549. Rheumatic Fever. Bacteriologic Studies of a Non-Methemoglobin-Forming Streptococcus with Special Reference to its Soluble Toxin Production.
27. Kaiser, A. D., J. Infect. Dis., 1928, xlii, 25. Skin Reactions in Rheumatic Fever.
28. Swift, H. S., Wilson, M. G., Todd, E. W., Am. J. Dis. Child., 1929, xxxvii, 98. Skin Reactions of Patients with Rheumatic Fever to Toxic Filtrates of Streptococcus.
29. Swift, H. F., Hitchcock, C. H., and Derick, C. L., Proc. Soc. Exp. Biol. and Med., 1928, xxv, 312. General Tuberculin-like Reactions in Rheumatic Fever Patients Following Intravenous Injections of Streptococcus Vaccines or Nucleo-proteins.
30. Swift, H. F., Derick, C. L., and Hitchcock, C. H., J. Am. Med. Assoc., 1928, xc, 906. Trans. Assoc. Am. Phys., 1928, xliii, 192. Bacterial Allergy (Hyperergy) to Nonhemolytic Streptococci. Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci.
31. Zinsser, H., and Yu, H., Arch. Int. Med., 1928, xlii, 301. The Bacteriology of Rheumatic Fever and the Allergic Hypothesis.
32. Schick, B., Jahrbch. f. Kinderheilkunde, 1907, lxv, 132. Die Nachkrankheiten des Scharlach.
33. von Pirquet, C. E., Arch. Int. Med., 1911, vii, 259, 383. Allergy.
34. Longcope, W. T., J. Exp. Med., 1913, xviii, 678. The Production of Experimental Nephritis by Repeated Proteid Intoxication.
35. Long, E. R., and Finner, L. L., Am. J. Path., 1928, iv, 571. Experimental Glomerular Nephritis Produced by Intrarenal Tuberculin Reactions.