STUDIES ON THE IMMUNE RESPONSE OF THE RHEUMATIC SUBJECT AND ITS RELATIONSHIP TO ACTIVITY OF THE RHEUMATIC PROCESS*

II. Observations on an Epidemic of Influenza Followed by Hemolytic Streptococcus Infections in a Rheumatic Colony

By ALVIN F. COBURN, M.D., and RUTH H. PAULI

(From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York)

(Received for publication, April 16, 1935)

Several bacteriological studies of outbreaks of acute rheumatism have been made in England. Sheldon (1) observed a series of severe recrudescences among the rheumatic children at Cheyne Hospital in the winter of 1930–31. Collis studied the throat flora of Sheldon's patients and reported (2) that out of thirty-two children with hemolytic streptococcus infections of the pharynx, twenty-four had rheumatic recrudescences. Bradley (3, 4) observed two severe outbreaks of acute rheumatism in English boarding schools, following epidemics of respiratory infections, both in 1929 and in 1931. The strains of hemolytic streptococcus associated with these three outbreaks were studied by Griffith (5). Agglutinin absorption tests showed that within each epidemic, the organisms from a number of patients were serologically identical but that the three epidemic strains were distinct. Collis's outbreak followed infections with the Carter strain (Griffith type 13). Bradley's two outbreaks followed epidemics with the Hutchinson strain in 1929 (Griffith type 18) and the Beatty strain in 1931 (Griffith type 17). Organisms antigenically identical with each of these three strains have been isolated in New York City from patients with pharyngitis, which was followed by severe attacks of acute rheumatism (5, 6). The purpose of the present paper is to

* The work reported in this communication was carried out under The Kellogg Foundation Fund.

record observations on a series of infections which occurred during the spring of 1934 at The Pelham Home, an institution for the convalescent care of children with heart disease.

The Host Group at The Pelham Home

The group under observation consisted of thirty-five girls between the ages of 6 and 16 with cardiac disease. One of these had congenital heart disease; the others were known to be rheumatic subjects. The tonsils had been removed in all but four. They had been, with a few exceptions, under the care of the authors for a period of 1 to 6 years. Each had had in the past either a frank rheumatic attack or a number of mild manifestations accompanied by the development of the auscultatory signs of mitral stenosis. Some of them had been at The Pelham Home for a period of several years; others were admitted only a few weeks before the commencement of school in September, 1933, when this particular study began. At that time some of the children had appeared free of rheumatic activity for more than 1 year; others were symptom-free but convalescent from a recent attack; others were experiencing mild manifestations of a subsiding disease process. All appeared in moderately good health. Living conditions were ideal with one exception, the close contact which might facilitate the rapid transmission of infection. The girls attended school in one room of The Pelham Home and slept in three dormitories, containing six, eleven and thirteen beds. They came in contact with their families once each month, and were exposed to the respiratory infections of a teacher and of seven individuals occupying rooms at The Pelham Home—four nurses, a cook, a maid and a janitor. They were all fed on a presumably adequate diet, with ample fresh fruit, fresh vegetables and milk, and sufficient calories to cause a considerable gain in weight in each individual. They were protected from dampness and yet had the opportunity to play almost every afternoon in the fresh air and sunshine. Extreme fluctuations in temperature were obviated by automatic thermostatic control of the building at approximately 70°F. during the day and 55°F. at night. The children were seen and questioned each morning by the nurse in charge of The Pelham Home. Rectal temperatures and pulse rates were recorded each morning and night. The patients received no medication other than cod liver oil. Physical examinations were made weekly, and the throat flora of each patient was cultured twice a week. The progress of the group throughout the year may be divided into two periods: September to March 20, March 20 through July.

The Epidemic of Influenza

Between September, 1933, and January, 1934, the health of the group of thirty children at The Pelham Home was unusually good. Seven individuals were restricted in activity because of evidence pointing to subsiding carditis. Four individuals contracted "colds"

which were not followed by rheumatic manifestations. During early January mild vague rheumatic symptoms were experienced by two individuals, occurring about 10 days after "colds." Eight other children contracted "colds" and four had chicken pox without developing rheumatic recrudescences. There was no evidence of active carditis in any member of the group. Four patients were discharged during the latter part of this period in excellent condition, the disease apparently inactive. The blood sedimentation rates (determined by Westergren's (7) modification of Fåhraeus' method) at the end of February were the lowest recorded for any group tested at any time at The Pelham Home (twenty-four below 20, three between 20 and 30 mm.). This corroborated the clinical impression of minimal rheumatic activity in this group of rheumatic children.

The phenomena which led to the second half of this study began on March 15, when the cook became critically ill with a temperature of 105° and prostration. The illness resembled epidemic influenza and lasted for 7 days. On March 20, two of the children became ill with this respiratory infection, and during the week eight others were prostrated. The symptoms were almost identical in all instances, consisting of malaise for 1 day followed by a 3 day fever rising to a peak of about 104°F. On the 2nd day the fever was accompanied by nausea, vomiting, aches, cephalalgia and pallor, followed by marked weakness for a few succeeding days. The intensity of the disease gradually diminished. The remainder of the group, with possibly six exceptions, were infected during April; however, the clinical picture in these children was that of a severe "cold" with only slight rise in temperature.

Outbreak of Secondary Infections

The first three patients to contract influenza recovered from this infection in 3 days. While convalescent, the first two individuals developed pharyngitis and the third tracheitis. The pharyngeal infections were not severe, were characterized by injection of the mucous membranes, edema and a little exudate, which persisted for only 2 or 3 days. Tracheitis was characterized by paroxysms of coughing and hoarseness. Altogether twelve patients, while convalescent from influenza, developed signs or symptoms of secondary

infection of the upper respiratory tract. In one child influenza was followed by severe bronchitis. Except for this patient all of the children were able to return to school 1 week after influenza. Later, two individuals, after having completely recovered from uncomplicated influenza and having been symptom-free for 2 weeks or more, contracted throat infections. Finally, five individuals who had entirely escaped influenza developed severe or mild pharyngitis.[1] During these infections there was only a slight increase in the blood sedimentation rate. An analysis of these respiratory infections revealed first a wave of typical severe influenza beginning precipitously on March 20, gradually becoming milder and complicated by a series of secondary infections of the upper respiratory tract. The earlier cases of secondary infection occurred during recovery from influenza; the later cases appeared independently. Bacteriological studies indicated that these two outbreaks of respiratory infection were due to two distinct agents.

Bacteriological Studies

Studies of the throat flora were conducted on each patient during the entire period of observation. Two cultures were taken each week from the surface of the tonsils or the tonsillar fossae. These were streaked on fresh rabbit blood agar plates; the growth was examined after 24 hours incubation at 37°C. The presence and number of organisms was recorded in uniform manner. All pathogens or potential pathogenic agents were studied in detail. In this way it was possible to know the character of the throat flora harbored by each individual, and it was usually possible to detect the arrival of new organisms at The Pelham Home.

The basic flora in the throats of all the patients at The Pelham Home during the fall months consisted of *Streptococcus viridans*, Gram-negative cocci, Bacillus X, staphylococci, diphtheroid bacilli and anhemolytic streptococci. A few individuals carried Pfeiffer bacillus, pneumococcus or hemolytic streptococcus in small numbers. The throat flora of the group showed no striking change during the winter months. Hemolytic streptococcus appeared in moderate numbers in

[1] Severe pharyngitis occurred in the individuals who had only recently developed rheumatism and in the non-rheumatic subject. The patients with rheumatic heart disease of long standing had extremely mild throat infections.

about one-third of the patients but was not the predominating organism in a single individual. These organisms formed glossy colonies on chocolate agar plates, produced no detectable skin toxin or streptolysin, and all fell into the group of Hemolytic III, according to Holman's classification based on sugar fermentation reactions. They did not appear to be associated with active disease.

At the onset of the epidemic of influenza a filterable virus was recovered from nasal washings (8) although the throat flora showed no changes. However, in the first two patients contracting influenza, hemolytic streptococcus appeared in their throat cultures during convalescence, at the time that they developed pharyngitis. Other individuals had completely recovered from influenza when they developed throat infections, and hemolytic streptococcus appeared in predominance during this pharyngitis. The change in throat flora was easily detected in individuals with infection of the pharynx, but was less definite in the children who developed bronchitis or tracheitis after influenza. In the former hemolytic streptococcus predominated; in the latter the organism was present in small numbers. The organisms associated with these secondary infections appeared to be a single type with the following characteristics: they formed matt (9) colonies on chocolate blood agar plates; were strong streptolysin producers; and fermented lactose and salicin but not mannite, falling into Holman's classification of *Streptococcus pyogenes*. These organisms seemed identical with each other, remained stable in blood broth and were culturally distinct from the other strain (Hemolytic III) which had been carried in the throats of a number of patients during the winter months, which did not produce detectable streptolysin or toxin, and which did not give rise to symptoms. All of the epidemic strains were found in this laboratory to produce strong skin toxins. Two of these, the organisms from Hallahan and Westwater, were studied more closely by Hooker. He tested their filtrates on suitable reactors and observed that both produced strong B toxin and weak A toxin. (See Reference 10.) The Hallahan strain caused a skin reaction 18 x 20 mm. in dilution 1:10,000 and 16 x 18 mm. in 1:15,000; the Westwater strain, 18 x 21 mm. and 18 x 19 mm. in these dilutions. Both toxins in dilution of 1:15,000 were completely neutralized by 1 N.D. (1/50 unit) of B containing scarlatinal antitoxin.

Hooker[2] considered "the Hallahan and Westwater strains toxigenically indistinguishable."

The following questions relating to the identity of these strains were investigated: (*a*) whether early and late epidemic strains were of a single serological type; (*b*) whether the patient with congenital heart disease was infected with the epidemic strain; (*c*) whether the epidemic strains were of the same serological type as the strain which had been carried in the throats previous to the epidemic; (*d*) whether the patient who developed pharyngitis and acute rheumatism shortly after discharge from The Pelham Home had been infected with the epidemic strain. Lancefield's (11) technique was employed for this study. This author has demonstrated that:

"HCl extracts of *Streptococcus hemolyticus* contain type-specific, as well as non-type-specific substances. The type-specific substance may be detected by the use of antibacterial sera absorbed with heterologous strains of hemolytic streptococcus. Such absorbed sera are type-specific. They are precipitated only by extracts of strains of the homologous types."

By the use of the precipitin test with absorbed serum it is possible to divide hemolytic streptococci into distinct serological types. The technique used in the present study was as follows:

(*a*) *Preparation of HCl Extracts.*—The extracts were prepared according to Lancefield's technique.

(*b*) *Technique of Immunization.*—The rabbit antisera were prepared as follows: Adult animals weighing between 2 and 3 kilos were first tested to rule out the presence of natural antibodies to streptococcus. They were immunized with heat-killed and then with living organisms over a period of 4 weeks. The organisms were obtained from 0.1 per cent dextrose broth, were washed in saline and preserved in merthiolate 1:10,000. A test bleeding was made on the 4th day after the last injection, and the animals killed on the 5th day. Four rabbits were immunized with each organism. The schedule is given on page 143.

The last six doses were supplemented with living 15 hour broth cultures. The broth was removed, culture washed and brought up to volume with saline and given in doses of 0.05 cc. at first and 0.1 cc. in the last four injections.

(*c*) *Absorption of Sera.*—Absorption of sera was carried out as follows: Bacteria from 1.5 liters of plain broth culture of heterologous (S 24, supplied by Dr. Lancefield) and a similar quantity of homologous organisms were centrifuged. The organisms in each instance were washed twice with saline, killed by heating at 58°C. and suspended in 2 cc. of saline for 1 hour. To each tube of bacteria 4 cc. of serum were added drop by drop and the mixture thoroughly shaken. The mixture was incubated in a 37° bath for 30 minutes, refrigerated for 3 hours, centrifuged and the serum removed. This serum was again added in the same way to a fresh suspension of bacteria. Absorption was repeated as before. The supernatant serum was then tested. Absorption was found complete in each instance.

[2] Personal communication.

Wk. 1, Day 1	Subcutaneous injection	0.5 cc. killed culture, 5 billion per cc.
" 1, " 2	" "	0.5 " " " 5 " " "
" 1, " 3	" "	0.5 " " " 5 " " "
" 1, " 4	Intraperitoneal "	1.0 " " " 1 " " "
" 1, " 5	" "	1.0 " " " 1 " " "
" 1, " 6	" "	1.0 " " " 1 " " "
" 2, " 1	Intravenous "	0.5 " " " 1 " " "
" 2, " 2	" "	0.5 " " " 1 " " "
" 2, " 3	" "	1.0 " " " 1 " " "
" 2, " 4	" "	1.0 " " " 1 " " "
" 3, " 1	" "	2.0 " " " 2 " " "
" 3, " 2	" "	2.0 " " " 2 " " "
" 3, " 3	" "	1.0 " " " 1 " " "
" 3, " 4	" "	1.0 " " " 1 " " "
" 4, " 1	" "	0.9 " " " 1 " " "
" 4, " 2	" "	0.9 " " " 1 " " "
" 4, " 3	" "	0.9 " " " 1 " " "
" 4, " 4	" "	0.9 " " " 1 " " "

Eight strains of hemolytic streptococcus were selected for this study. All of them were isolated during the first 48 hours of acute pharyngitis when they were present in large numbers in the throat cultures. Two strains, EpEH and EpEW obtained from Hallahan (page 166) and Westwater (page 164) were from the first two patients to become infected shortly after the outbreak of influenza. Three strains, EpEF, EpER and EpEP were obtained from Fay (page 165), Raimonde (page 164) and Patterson (page 168) who contracted pharyngitis entirely independent of influenza. Strain NEP, glossy, was present in the throat of Patterson previous to the influenza epidemic and was representative of the Hemolytic III organisms carried by a number of patients during the winter months. Strain EpS was cultured from the throat of Sucich (page 173) during pharyngitis contracted at the time that strains EpER and EpEP were recovered. Strain E 112, matt, was cultured from the throat of Ferrara (page 149) during pharyngitis which developed 2 weeks after the patient was discharged from The Pelham Home. The results of the precipitin tests of strains from the first two and last two patients to be infected during the epidemic and of two strains not associated with the epidemic are presented in Table I *A*, *B* and *C*. With the exception of EpER all of the rabbit sera were of unusually good titer.

From the data presented in Table I *A*, *B* and *C* it is seen that precipitin reactions occurred between HCl extracts of the Ep (epidemic) strains and their unabsorbed and heterologously absorbed sera. There were no reactions between their HCl extracts and their homologously

TABLE I

Precipitin Reactions of Strains of Hemolytic Streptococcus Recovered from Pelham Home Patients

A

HCl extract	Rabbit serum EpEH (Diluted 1:1)			Rabbit sera	HCl extract EpEH		
	Unabsorbed	Absorbed with strain			Unabsorbed	Absorbed with strain	
		Homologous	Heterologous			Homologous	Heterologous
EpEH	+ ++ ++	− − −	+ ++ ++	EpEH	+ ++ ++	− − −	+ ++ ++
EpEW	+ + ++	− − −	− + +	EpEW	− ± +	− − −	− ± +
EpER	+ + +	− − −	− − −	EpER	− − −	− − −	− − −
EpEF	− − ++	− − −	− − ++	EpEF	− ± ++	− − −	− ± ++
EpEP	− ++ ++	− − −	− ++ ++	EpEP	− ++ ++	− − −	− ++ ++
EpS	− + +	− − −	− ± ±	EpS	+ − +	− − −	− − +
NEP	− − −	− − −	− − −	NEP	− − −	− − −	− − −
E 112	− − −	− − −	− − −	E 112	− − −	− − −	− − −
	Rabbit serum EpEW				HCl extract EpEW		
EpEW	+ + +	− − −	− + +	EpEW	+ + +	− − −	− + ++
EpEH	− ± +	− − −	− ± +	EpEH	+ + ++	− − −	− + +
EpER	− − ±	− − −	− − ±	EpER	− − −	− − −	− − −
EpEF	± + +	− − −	− ± +	EpEF	+ + +	− − −	− + +
EpEP	− ± +	− − −	− − +	EpEP	+ ++ +	− − −	− ++ +
EpS	− − ±	− − −	− − ±	EpS	+ − +	− − −	− − −
NEP	− − −	− − −	− − −	NEP	− − −	− − −	− − −
E 112	− − −	− − −	− − −	E 112	− − −	− − −	− − −

B

	Rabbit serum EpEP				HCl extract EpEP		
EpEP	+ ++ ++	− − −	− − ++	EpEP	+ ++ ++	− − −	− − ++
EpEH	− ++ ++	− − −	− ++ +	EpEH	− ++ ++	− − −	− ++ ++
EpEW	+ ++ +	− − −	− ++ +	EpEW	− ± +	− − −	− ± +
EpER	− ± +	− − −	− − −	EpER	− − −	− − −	− − −
EpEF	± + ++	− − −	− + ++	EpEF	− ± +	− − −	− ± +
EpS	− + +	− − −	− − ±	EpS	− − −	− − −	− − −
NEP	− − +	− − −	− − −	NEP	− − −	− − −	− − −
E 112	− − −	− − −	− − −	E 112	− − −	− − −	− − −
	Rabbit serum EpS				HCl extract EpS		
EpS	+ ++ ++	− − −	− ++ ++	EpS	+ ++ ++	− − −	− ++ ++
EpEH	+ − +	− − −	− − ±	EpEH	− + +	− − −	− ± ±
EpEW	+ − +	− − −	− − −	EpEW	− − −	− − −	− − −
EpER	+ + ++	− − −	− + ++	EpER	− ++ ++	− − −	− + +
EpEF	+ − +	− − −	− ± ++	EpEF	− − ±	− − −	− − ±
EpEP	− − −	− − −	− − −	EpEP	− + +	− − −	− − ±
NEP	− − −	− − −	− − −	NEP	− − −	− − −	− − −
E 112	− − −	− − −	− − −	E 112	− − −	− − −	− − −

The determinations indicate three readings; first, made at 20 minutes at room temperature; second, after 2 hours incubation at 37.5°C.; third, after 18 hours in the ice box, not centrifuged.

TABLE I—*Concluded*

C

HCl extract	Rabbit serum NEP						Rabbit sera	HCl extract NEP					
	Unabsorbed			Absorbed with strain				Unabsorbed			Absorbed with strain		
				Homologous		Heterologous					Homologous		Heterologous
NEP	+	++	++	−	−	−	+	++	++	NEP	+	++	++	−	−	−	+	++	++
EpEH	−	−	−	−	−	−	−	−	−	EpEH	−	−	−	−	−	−	−	−	−
EpEW	−	−	−	−	−	−	−	−	−	EpEW	−	−	−	−	−	−	−	−	−
EpER	−	−	−	−	−	−	−	−	−	EpER	−	−	−	−	−	−	−	−	−
EpEF	−	−	−	−	−	−	−	−	−	EpEF	−	−	−	−	−	−	−	−	−
EpEP	−	−	−	−	−	−	−	−	−	EpEP	−	−	−	−	−	−	−	−	−
EpS	−	−	−	−	−	−	−	−	−	EpS	−	−	−	−	−	−	−	−	−
E 112	−	−	−	−	−	−	−	−	−	E 112	−	−	−	−	−	−	−	−	−
	Rabbit serum E 112							HCl extract E 112					
E 112	−	+	++	−	−	−	−	+	++	E 112	−	+	++	−	−	−	−	+	++
EpEH	−	−	−	−	−	−	−	−	−	EpEH	−	−	−	−	−	−	−	−	−
EpEW	−	−	−	−	−	−	−	−	−	EpEW	−	−	−	−	−	−	−	−	−
EpER	−	−	−	−	−	−	−	−	−	EpER	−	−	−	−	−	−	−	−	−
EpEF	−	−	−	−	−	−	−	−	−	EpEF	−	−	−	−	−	−	−	−	−
EpEP	−	−	−	−	−	−	−	−	−	EpEP	−	−	−	−	−	−	−	−	−
EpS	−	−	−	−	−	−	−	−	−	EpS	−	−	−	−	−	−	−	−	−
NEP	−	−	−	−	−	−	−	−	−	NEP	−	−	−	−	−	−	−	−	−

absorbed sera. The absence of specific reactions between the sera and HCl extracts of Ep strains and the extracts or sera of the other organisms clearly defined hemolytic streptococcus EpEH, EpEW, EpER, EpEF, EpEP and EpS as belonging to one group. Likewise the absence of reactions showed that Strain NEP and Strain E 112 were each antigenically different from the epidemic strains.

The results of the tests are believed to indicate: (*a*) that all of the epidemic strains, including both those isolated from infections during influenza (Table I *A*) and those isolated from infections independent of influenza (Table I *B*) were a single strain; (*b*) that Strain EpS, infecting a non-rheumatic subject, was indistinguishable from the other five epidemic strains; (*c*) that all of the epidemic strains were antigenically distinct from the Strain NEP (Table I *C*), which had been prevalent before the onset of the epidemic; (*d*) that Strain E 112 (Table I *C*) was antigenically different, both from the six epidemic strains and also

from the carrier strain. Classification of these six epidemic strains by the use of Lancefield's (11) technique showed that they all fell into our (6) group VI, Griffith's Type 2*b*, and were antigenically different from the English epidemic strains (page 137). E 112 was indistinguishable from Griffith's Beatty strain, Type 17, our group V.

In summary, the bacteriological study of the throat flora at The Pelham Home showed the presence of two pathogenic agents operating among an isolated group of rheumatic children. These individuals had experienced good health for a long period of time before the onset of infection. A few of them were carriers of an apparently nonpathogenic strain of hemolytic streptococcus before the epidemic, and in two of these there had occurred mild recrudescences following "colds;" however, these children had recovered by the middle of March. At that time there occurred an outbreak of typical influenza, which waned in its intensity but which nevertheless during a period of 3 weeks incapacitated all but four of the thirty children. This infection was probably due to the filterable virus recovered from Raimonde (8). Within a week after the appearance of the influenza a new strain of hemolytic streptococcus appeared at The Pelham Home. It was easily recognized on the 1st day of its manifestations. Unlike the carrier strain, it was associated with acute respiratory infection. At first it seemed to be transmitted only with the help of influenza. At the end of 2 weeks it appeared in the throats of contacts who had escaped influenza, where it caused severe infections. At this time the strain seemed highly communicable and independent of the filterable virus. Four weeks after the subsidence of influenza, hemolytic streptococcus was present in the throat flora of all but two of the group. The serological tests showed that the epidemic (Ep) strains were of a single type, and were antigenically different both from the non-effective (NE) carrier strain and from another effective (E)[3] strain acquired by a Pelham Home patient shortly after arrival in New York City.

[3] The term "effective" has been applied by the authors to strains of hemolytic streptococcus recovered from throat infections which were followed by rheumatic recrudescences in susceptible subjects. Detailed studies on the characteristics of effective (E) and non-effective (NE) strains are to be reported in Paper IV of this series (*J. Clin. Inv.*, 1935, in press).

The Epidemic of Rheumatic Fever

Suddenly on April 10, 3 weeks after the onset of influenza, three patients in adjoining beds showed a marked rise in body temperature. All of these individuals had recovered from influenza and secondary infections by April 1. The cause of pyrexia was definitely established during the 2nd week of April, when each of these three children developed fulminating pancarditis. A few days later seven others of the group who had had streptococcus infections changed from a state of

TABLE II

The Relationship of Respiratory Infections to the Development of Rheumatic Recrudescences

Type of respiratory infection	No. of cases	Type of rheumatic attack	No. of cases
No respiratory infection	3	None	3
Influenza without hemolytic streptococcus infection	4	None	4
Influenza complicated by hemolytic streptococcus infection	11	Severe attacks	7
		Mild attacks	2*
		No attack	2
Influenza followed after an interval by hemolytic streptococcus infection	2	Severe attacks	2
Hemolytic streptococcus infection without influenza	5	Severe attacks	2
		Mild attacks	2
		No attack	1†

* One atypical attack.

† Non-rheumatic subject.

good health to one of critical illness. Each of these rheumatic attacks began between 10 and 14 days after the subsidence of the secondary infection. During the latter half of April and early part of May five more children, all but one of whom had had influenza, contracted throat infections. Four of them developed rheumatic attacks between May 8 and May 18. The fifth, a non-rheumatic subject with congenital heart disease, remained symptom-free. One more case of pharyngitis developed on May 15, and was followed by a severe rheumatic attack in June. Three of the 6 attacks beginning in May and

June appeared from 22 to 24 days after the throat infection; however, in one case the pulse, in another the sedimentation rate, in the third the antistreptolysin titer, had been elevated for 10 to 14 days in advance of acute symptoms. Three children who had escaped all respiratory infections and four others who had contracted only influenza, did not develop rheumatic fever. The relationship of these infections to rheumatic recrudescences is summarized in Table II.

TABLE III

Antistreptolysin Titers (in Units) of Twenty Children at The Pelham Home

Patient	Fall, 1933	Winter, 1934
Allen, G.	143	125
Carroll	125	125
Cleary	143	125
Curnan	71	50
Fay	33	33
Ferrara	63	63
Goch	71	63
Gross	56	33
Gunning*	83	200
Hudson	200	200
Kienzle*	167	250
Kiernan	143	125
Libera	143	143
Marten	56	56
Patterson	143	71
Raimonde	500	143
Ryan	167	125
Torres	167	143
Westwater	125	100
Williamson	71	63

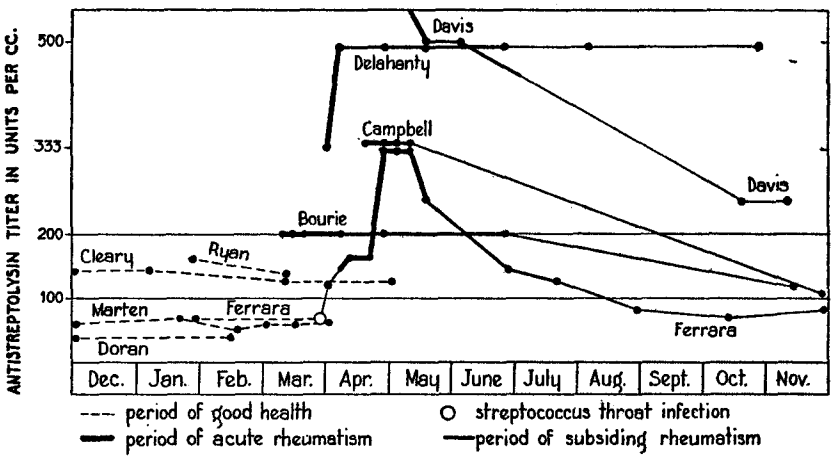
* These were the two children who had mild recrudescences in February, 1934 about 6 weeks before the epidemic.

Immunological Studies

The findings to be presented in a later paper of this series show a close relationship between hemolytic streptococcus infection and a rise[4] of the antistreptolysin titer in the blood serum. In this con-

[4] The development of antibody to hemolytic streptococcus coincident with the onset of the rheumatic attack has been pointed out in England (12) (precipitins) and by the authors (13) (antistreptolysin).

nection the authors were particularly interested in following the titer of this antibody in the group at The Pelham Home. During the 6 months period of observation previous to the epidemic, there had been a downward trend in the antistreptolysin titer of all but two individuals. These determinations are shown in Table III. The patients discharged in good health just before or during the epidemic had low titers (Ryan, Cleary, Marten and Doran). Those who were admitted in their places had active rheumatism and high titers (Davis, Delahanty, Campbell and Bourie). One individual (Ferrara) was infected with hemolytic streptococcus shortly after discharge from The Pelham Home and readmitted with acute rheumatism.[5] The antistreptolysin curves are presented in Text-fig. 1. The antistreptolysin titer levels changed in many of The Pelham Home children following the outbreak of hemolytic streptoocccus infections. For purposes of comparison the patients' titers will be considered in six groups: (1) those who escaped influenza and streptococcus infection; (2) those who contracted influenza and escaped streptococcus infection; (3) those who contracted streptococcus infection with or without influenza but who escaped typical rheumatic attacks; (4) those who contracted strep-



TEXT-FIG. 1. Patients discharged from The Pelham Home before the epidemic and new patients admitted to The Pelham Home during the epidemic.

[5] This observation has been made each year in the group of children returning to their families in New York City during the late winter months.

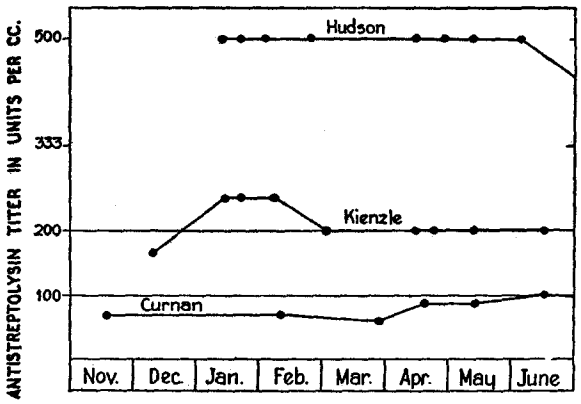
tococcus infection with or without influenza and developed mild rheumatic attacks; (5) those who contracted streptococcus infection while convalescent from influenza and developed severe rheumatic attacks; (6) those who contracted streptococcus infection independent of influenza and developed severe rheumatic attacks.

1. Antistreptolysin Titers of Patients Escaping Influenza and Streptococcus Infection.—Three individuals escaped respiratory infection during the spring months at The Pelham Home. One patient, Hudson, had been admitted with subsiding rheumatism in January. The other two patients, Kienzle and Curnan, had been at The Pelham Home for a period of years. The titer levels showed little or no change following the epidemic, and the patients remained in excellent health. The titer curves are presented in Text-fig. 2.

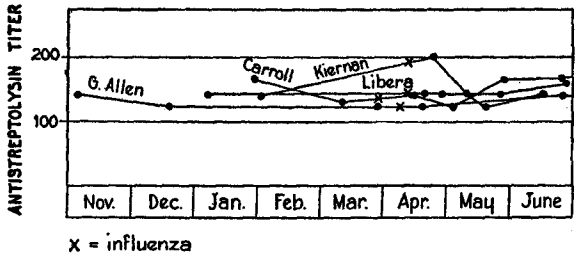
2. Antistreptolysin Titers of Patients Contracting Influenza and Escaping Streptococcus Infection.—Four individuals contracted influenza but escaped streptococcus infection. All had been at The Pelham Home for a long period of time. The titer levels showed little or no change following the epidemic. This was in accord with previous observations on rheumatic patients recovering from influenza. After recovery from influenza the patients remained in excellent health. The titer curves are presented in Text-fig. 3.

3. Antistreptolysin Titers of Patients Contracting Streptococcus Infection but Escaping Acute Rheumatism.—Four individuals contracted streptococcus infection but failed to develop typical rheumatic attacks. In three of them the streptococcus infections followed influenza. One patient, Sucich, was a non-rheumatic subject; another, McMahon, was an atypical rheumatic subject. There were only moderate rises in antistreptolysin titer. The responses of these individuals will be considered in the following paper. The antistreptolysin curves are presented in Text-fig. 4.

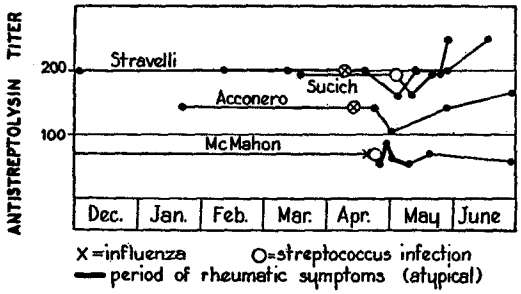
4. Antistreptolysin Titers of Patients Contracting Streptococcus Infection with or without Influenza and Developing Mild Rheumatic Attacks.—Three individuals contracted streptococcus infections which were followed by mild rheumatism. Patients Grabeck and Gross had escaped influenza. All three children developed a definite rise in antistreptolysin titer with the onset of rheumatic symptoms. The titer curves are presented in Text-fig. 5.



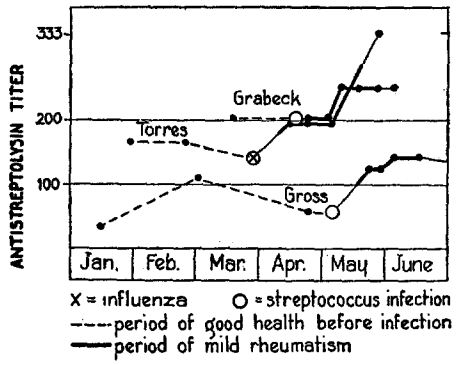
TEXT-FIG. 2. Three patients who contracted no infection at all during the epidemic.



TEXT-FIG. 3. Four patients who contracted influenza which was not followed by hemolytic streptococcus infection.



TEXT-FIG. 4. Four patients who did not develop typical rheumatic fever following infection with hemolytic streptococcus.

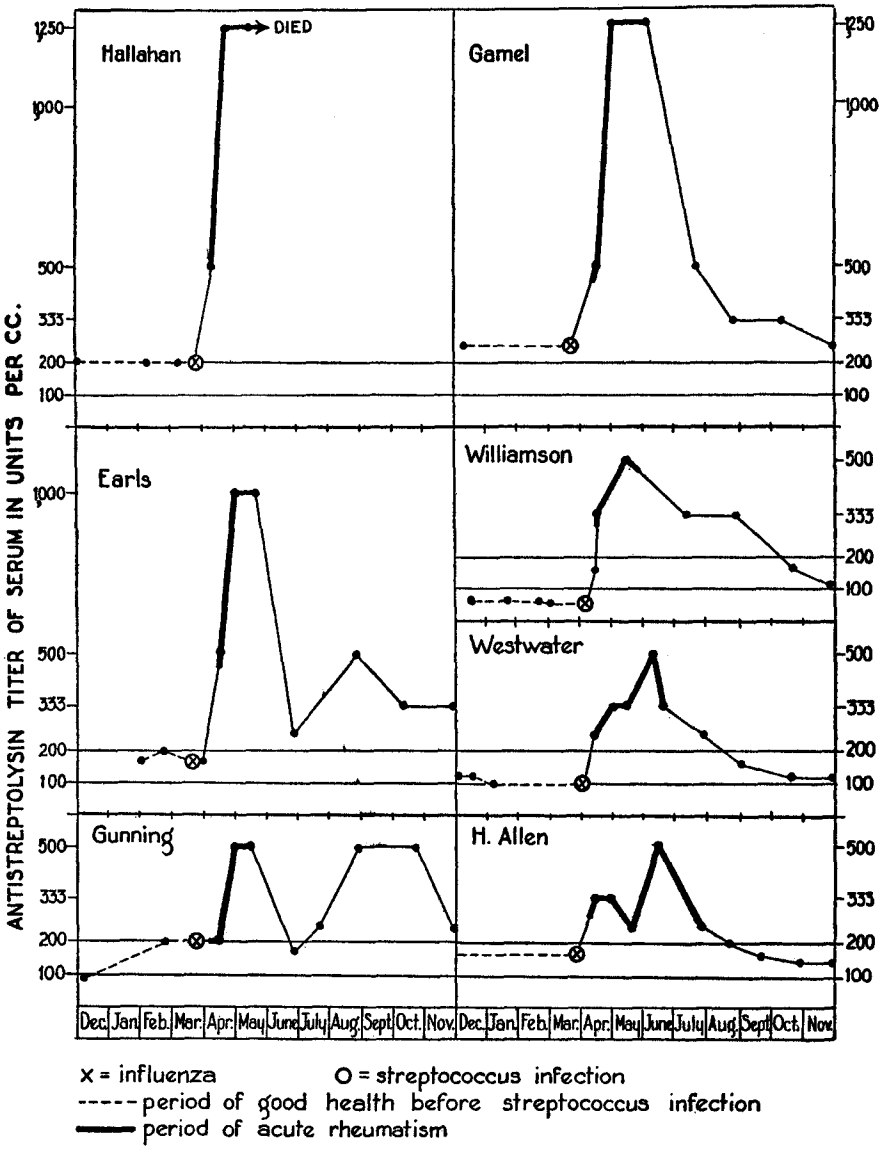


TEXT-FIG. 5. Three patients with mild attacks.

5. Antistreptolysin Titers of Patients Who Contracted Both Influenza and Streptococcus Infection and Then Developed Severe Rheumatic Attacks.—Seven patients contracted influenza which was complicated by streptococcus infection. All developed severe rheumatic attacks. In every case, the antistreptolysin titer showed a marked rise at the onset of rheumatic manifestations. The titer curves are presented in Text-fig. 6.

These seven patients developed rheumatic attacks in rapid succession. Each was preceded by upper respiratory tract infections. The infections appeared to be due to two distinct agents—first, a filterable virus causing influenza; second, hemolytic streptococcus causing a variety of respiratory symptoms. In those individuals who developed infection of the pharynx while recovering from influenza, it was possible to see the inflammatory reaction and to obtain hemolytic streptococcus in almost pure culture. In others with tracheitis and bronchitis, the organisms were also recovered but in small numbers. Each patient developed a marked rise in antistreptolysin titer. However, in none of these instances could influenza be eliminated as a possible causative agent in the subsequent severe attacks of pancarditis.

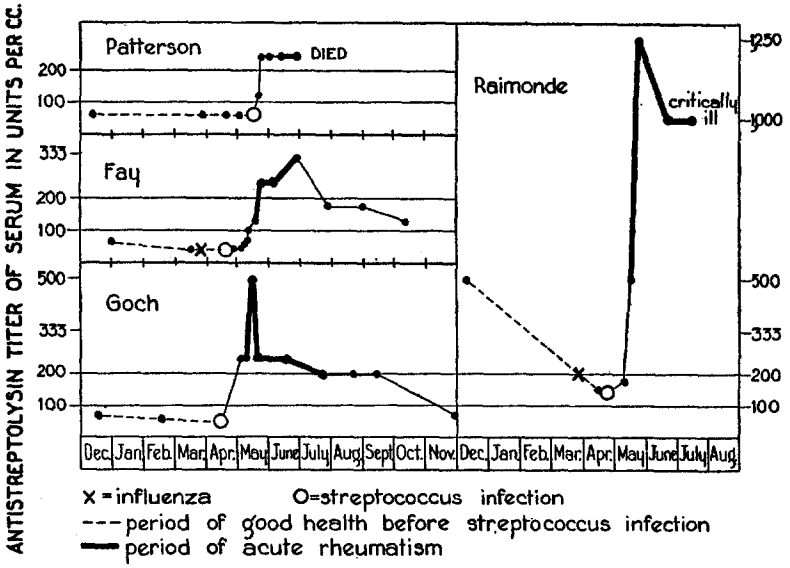
6. Antistreptolysin Titers of Patients Contracting Streptococcus Infections Independent of Influenza and Developing Severe Rheumatic Attacks.—Four patients who had been at The Pelham Home throughout the period of this study contracted streptococcus infection in



TEXT-FIG. 6. Seven patients with severe attacks following hemolytic streptococcus infection coincident with influenza.

April or May. In each instance this infection occurred independently of influenza. All developed rheumatic attacks of great severity. The onset of these attacks was either accompanied by or just preceded by a sharp rise in antistreptolysin titer. The titer curves are presented in Text-fig. 7.

These four patients contracted hemolytic streptococcus pharyngitis after the influenza epidemic had subsided. Two of these children, Raimonde and Fay, had recovered from influenza during the last week



TEXT-FIG. 7. Four patients with severe attacks following hemolytic streptococcus infection independent of influenza.

in March. The others, Goch and Patterson,[6] had escaped influenza but contracted hemolytic streptococcus pharyngitis at a later date. These infections were all followed by severe rheumatic attacks. One was fatal; and it is doubtful whether the other three individuals will recover. The antistreptolysin titer remained level following influenza and did not rise until the 2nd week after streptococcus infection. From patient Raimonde a filterable virus was recovered (8) during

[6] Patterson's antistreptolysin titer rose to 250 units at the onset of the rheumatic attack. A blood sample was not obtained during the 2nd week of the illness because of her critical condition.

influenza, and hemolytic streptococcus was not present in the throat cultures. Four weeks later the antistreptolysin titer had remained stationary. Then during pharyngitis, hemolytic streptococcus was predominant in the throat flora. This infection was followed after 2 weeks by a rise in antistreptolysin titer and acute rheumatism. Likewise the antistreptolysin determinations in the other patients corroborated the clinical and bacteriological findings, which indicated that influenza was not the etiological agent involved in this outbreak of rheumatic attacks.

DISCUSSION

This epidemic infection made it possible to observe the mass response of an isolated colony of rheumatic subjects to distinct pathogenic agents. That the chicken pox virus alone did not activate the rheumatic process was definite. Four children, all highly susceptible subjects, contracted chicken pox during the winter months. The throat flora remained free of hemolytic streptococcus; the antistreptolysin levels remained constant; no patient developed a single rheumatic manifestation. The influence of influenza was at first difficult to assess. The early cases of acute rheumatism had all had influenza accompanied by activity of the secondary invader, hemolytic streptococcus. All developed severe rheumatic attacks coincident with a sharp rise in antistreptolysin titer. From these patients it was not possible to exclude the influenza virus as a possible causative agent. However, other patients who contracted influenza at the same time and who escaped streptococcus infection responded differently. The antistreptolysin titer did not rise, and the rheumatic process remained quiescent in these individuals. Furthermore, two of these individuals subsequently became infected with the epidemic strain of hemolytic streptococcus, as late as 1 month after recovery from influenza. These streptococcus infections were then followed by a sharp rise in antistreptolysin titer and severe rheumatic attacks. Finally, two patients who had escaped influenza, yet who contracted pharyngitis with hemolytic streptococcus, developed fulminating rheumatic attacks with rapid death in one instance. For these reasons it seemed that influenza was significant, so far as rheumatism was concerned, only in facilitating the spread of streptococcus infection.

The character of the streptococcus infections changed during the

course of the epidemic. At first they were all mild and difficult to distinguish clinically from influenza. Some of the later infections were well defined and severe. These occurred in individuals who had previously experienced not more than one rheumatic attack. Whether the severity of the local infection was increased as a result of passage of the strain of streptococcus was unknown; nevertheless it was seen that the organism's effectiveness in initiating rheumatic activity was not altered. Streptococcus infections closely associated with influenza were neither more nor less effective in initiating rheumatic activity than uncomplicated pharyngitis. As influenza subsided, the epidemic strain of streptococcus was transmitted independently.

Finally, the cultural and serological tests showed that the outbreak of acute pharyngitis was due to a single strain of hemolytic streptococcus. Although it was not possible to trace the origin of this strain,[7]

[7] Since writing these papers the authors have had an unusually good opportunity to trace the origin and spread of one streptococcus infection, and to analyze the development of an immune response and the initiation of rheumatic activity. This observation may be summarized briefly.

Patient D. was admitted to The Pelham Home October, 1934, with subsiding rheumatic fever, large tonsils and hemolytic streptococcus in the throat flora. She carried this organism during the winter months apparently without spreading infection. On Apr. 20, 1935, she contracted the common cold, then prevalent at Pelham Home, and was kept in bed at one end of the ward because of severe coughing. On Apr. 22 hemolytic streptococcus increased in her throat flora to almost pure culture. The antistreptolysin titer was 333 units at this time and remained constant for 2 months. The patient escaped a rheumatic recrudescence.

Patient E. was also at Pelham Home during the same period, had no tonsils and no hemolytic streptococci in the throat flora. She contracted the common cold but escaped a rheumatic attack in April, 1935. However, her bed was next to the one occupied by D. On Apr. 26, E. contracted acute pharyngitis with hemolytic streptococcus in almost pure culture. The organism was indistinguishable from that of D (both Griffith Type I). E.'s antistreptolysin titer which had been 250 units, rose to 333 units on May 1, coincident with the development of a recrudescence. 2 weeks later there was another rise to 500 units, and the patient was transferred to Babies Hospital with rheumatic carditis of moderate severity.

It is the authors' opinion that the common cold was probably responsible for the change described in D.'s throat flora, for the severe coughing, and thus for the spreading of D.'s strain to E. The failure of D. to develop a rheumatic attack in the absence of antistreptolysin rise, and the development of a severe recrudescence coincident with the rise in circulating antibody in E. are in accord with the

it was antigenically distinct from the non-effective strain which had been carried in the throat flora previous to the epidemic.

SUMMARY

The observations presented in this paper may be summarized as follows:

A study has been made on an isolated group of children with heart disease.

All of these individuals, with one exception, were rheumatic subjects.

Many of them carried a strain of hemolytic streptococcus in the throat flora during the winter of 1934. The organism produced no detectible toxin and was not associated with respiratory disease.

Four patients contracted chicken pox during the winter months. None developed rheumatic recrudescences.

All of the individuals were in good health on March 1.

A severe epidemic of influenza began on March 22. All but six children contracted the disease. The filterable virus responsible for this outbreak was recovered.

This agent did not activate the rheumatic process. It was followed by an outbreak of streptococcus infection and appeared to facilitate its spread.

The source of these infections was not traced. They were due to a single type of hemolytic streptococcus which was a strong toxin producer. Its cultural, biochemical and serological characteristics were different from those of the carrier strain.

Of seventeen individuals proven bacteriologically to be infected with the epidemic strain, fourteen rheumatic subjects developed acute rheumatism, two rheumatic subjects and one patient with congenital heart disease escaped.

These fourteen rheumatic attacks were accompanied by a rise in antistreptolysin titer coincident with the onset of symptoms.

In four of these attacks it was possible to exclude influenza as a causative factor.

---

observations described in these papers. Whether the presence of infected tonsils served to modify the immune response and to protect D. from a recrudescence is unknown. Both patients had received 200 cc. of orange juice daily during 1935 in addition to an adequate diet.

The clinical observations, the bacteriological findings and the immunological evidence indicate that this severe outbreak of rheumatic fever was caused by *Streptococcus hemolyticus*, which appeared to be a single strain by type.

BIBLIOGRAPHY

1. Sheldon, W., *Lancet*, 1931, **1**, 1337.
2. Collis, W. R. F., *Proc. Roy. Soc. Med.*, 1932, **25**, 1631.
3. Bradley, W. H., *Proc. Roy. Soc. Med.*, 1932, **25**, 1635.
4. Bradley, W. H., *Quart. J. Med.*, 1932, **1**, N. S., 79.
5. Griffith, F., *J. Hyg.*, 1935, **34**, 542.
6. Coburn, A. F., and Pauli, R. H., *J. Exp. Med.*, 1932, **56**, 633.
7. Fåhraeus, R., *Phys. Rev.*, 1929, **9**, 241.
8. Dochez, A. R., Mills, K., and Kneeland, Y., Jr., *Proc. Soc. Exp. Biol. and Med.*, 1934, **32**, 406.
9. Todd, E. W., *Brit. J. Exp. Path.*, 1928, **9**, 1.
10. Hooker, S. B., and Follensby, E. M., *J. Immunol.*, 1934, **27**, 177.
11. Lancefield, R., *J. Exp. Med.*, 1928, **47**, 91.
12. Schlesinger, B. E., and Signy, A. B., *Quart. J. Med.*, 1933, **2**, N. S., 255.
13. Coburn, A. F., and Pauli, R. H., *J. Exp. Med.*, 1932, **56**, 651.