

Temporal Association of the Appearance of Mucoïd Strains of *Streptococcus Pyogenes* With a Continuing High Incidence of Rheumatic Fever in Utah

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ABSTRACT. *Objective.* Our objective was to confirm an observed temporal association of increased numbers of rheumatic fever cases concomitant with the appearance of an increased prevalence of mucoïd strains of *Streptococcus pyogenes*. During the resurgence of rheumatic fever (RF) that has occurred in the Intermountain area surrounding Salt Lake City, Utah, since 1985, the largest number of cases occurred in 1985 and 1986 and 12 years later in 1997 and 1998. During the initial outbreak and the later exacerbation of the resurgence, an increased number of mucoïd strains of *S pyogenes* were present in the community.

Methods. The referred cases of RF that fulfilled Jones criteria have been systematically reviewed by the medical staff at Primary Children's Medical Center yearly since 1985. Before the resurgence of RF, a program was initiated by the microbiology laboratory at Primary Children's Medical Center to store frozen isolates of *S pyogenes*. All frozen specimens were randomly selected and entered into a log; the coded entry allowed for comments regarding the origin of the isolate and whether the isolate had a mucoïd appearance on the blood agar culture plate. This log was reviewed in October 2002 to determine whether the percentage of frozen mucoïd isolates stored during the resurgence of RF would support the clinical and epidemiologic suspicion that mucoïd isolates seemed to be present with a higher frequency during the 2 periods of high incidence of RF. The percentage of mucoïd isolates was compared with the yearly number of cases of RF. A Pearson *r* correlation analysis was completed to determine whether there was a significant association between the percentage of mucoïd isolates and the number of cases of RF.

Results. The highest number of cases of RF was temporally associated with the highest percentage of mucoïd isolates. There was statistically significant correlation

between percentage of mucoïd strains and the number of RF cases.

Conclusions. The Utah experience with the resurgence of RF in a civilian population during the last decade and a half of the 20th century confirmed the temporal association of mucoïd strains of *S pyogenes*, primarily M-type 18, with a high incidence of RF. *Pediatrics* 2004;113:e168–e172. URL: <http://www.pediatrics.org/cgi/content/full/113/3/e168>; *rheumatic fever, mucoïd strains, Streptococcus pyogenes*.

ABBREVIATIONS. PCMC, Primary Children's Medical Center; RF, rheumatic fever; WHO, World Health Organization; LHBP, Laboratory of Human Bacterial Pathogenesis.

During the 1970s and early 1980s, the staff at Primary Children's Medical Center (PCMC) in Salt Lake City, Utah, like the rest of the United States, witnessed a striking decline in the number of cases of rheumatic fever (RF) compared with the numbers encountered during the mid 1950s and early 1960s. In 1985, a sudden and unanticipated resurgence of RF occurred when 61 cases were referred to the staff at PCMC.¹ An additional 41 cases were evaluated in 1986. This initial 2-year experience represented a 10-fold increase in the number of cases seen per year during the previous decade (average 5 cases per year).

After our initial report of this resurgence, isolated outbreaks of RF were reported from 3 children's hospitals^{2–4}; 2 military installations^{5,6}; and communities in Texas,⁷ West Virginia,^{8,9} Tennessee,^{10,11} New York,¹² and Alabama.¹³ Although probably an increase did occur during the late 1980s and early 1990s,¹⁴ some questioned a nationwide resurgence of RF.¹⁵ In contrast to the experience in Utah, the other isolated outbreaks reported during the late 1980s and early 1990s apparently have not persisted into the late 1990s except, perhaps, for the state of Colorado.¹⁶

In Utah, a second increase in cases of RF occurred in 1997 and 1998. During 1997, 41 cases were referred to PCMC, and in 1998, an alarmingly high number of cases (78) of RF were evaluated. During the 2 periods of highest incidence (1985–1986 and 1997–1998), the laboratory personnel at the microbiology laboratory at PCMC observed an increased number of group A streptococcal isolates with a mucoïd appearance to

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the colonies on the sheep blood agar culture plates. The present report describes the striking temporal association of a high incidence of RF with the appearance of increased numbers of mucoid strains of *Streptococcus pyogenes*, predominantly M-type 18, in Utah.

METHODS

Since 1985, the medical staff has performed a yearly review of all cases of RF referred to PCMC. Clinical, laboratory, echocardiographic, and demographic data were collected and compiled from all patients who fulfilled the revised or updated Jones criteria.^{17,18} Demographic data included the date of birth, age of onset of RF, address with zip code, and family history. All patients were asked whether they had experienced an antecedent sore throat, whether medical attention had been sought, whether a culture had been taken, and about their compliance in taking the prescribed antibiotics. Throat-swab specimens were obtained from the referred patients when they had not received antibiotics within 24 hours of being seen by the staff. At PCMC's microbiology laboratory, throat swabs from referred patients and from PCMC patients were plated onto 5% defibrinated sheep-blood agar plates. After incubation at 37°C for 18 hours in an atmosphere with reduced oxygen tension, β -hemolytic colonies were identified. The organisms were grouped with the use of fluorescent antibody microscopy or antibody-coated latex particles.

In 1983, the PCMC microbiology laboratory initiated a program to freeze and store pathogenic bacteria from 2 sources: body sites considered otherwise to be sterile and the throat specifically for *S pyogenes* from pharyngeal cultures. The primary purpose of the program was to have isolates available for antibiotic sensitivity studies and for *S pyogenes* screening kit evaluations. The *S pyogenes* isolates were deep frozen in skim milk with liquid nitrogen and then stored at -70°C. The frozen specimens were entered into a log coding each entry and allowing space for comments to indicate the origin of the isolate and whether there was a mucoid appearance on the culture plate. This log was examined for the first time in October 2002 to determine whether the observation concerning mucoid colonies of isolates obtained from the community would confirm the hypothesis that mucoid strains were encountered in increased numbers during the times of highest incidence of RF.

The varying number of stored frozen isolates shown in Table 1 deserves comment. The freezer space reserved for *S pyogenes* became filled in 1992 and could not accommodate additional isolates unless specimens had been removed for study. In 1997, a second freezer became available exclusively to store *S pyogenes* isolates, which allowed the larger number to be stored in the later

years of the study. It should be stressed that at no time was there any preselection as to which group A isolates were to be stored. The selection depended solely on the availability of space, which specimens were present in the laboratory at the time, and the time available for the laboratory technicians to complete a task of low priority.

In 1986, cultures were also obtained from 6 siblings of 4 patients with RF and from randomized healthy school children in 3 Utah communities that reported RF cases. In 1986 and also in 1998, isolates were sent to the World Health Organization (WHO) Collaborating Center for Reference and Research on Streptococci at the University of Minnesota, where serologic grouping and typing were conducted using standard techniques. In 1999, a total of 947 pharyngeal isolates, mucoid and nonmucoid, that were recovered from the community between 1984 and 1999 were submitted for genetic and biochemical studies conducted at the Laboratory of Human Bacterial Pathogenesis (LHBP) Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health (Hamilton, MN).

During 1999 and 2000, RF patients who had been seen in 1985 and 1986 were contacted to return for a follow-up evaluation, which included signing an Institutional Review Board consent and/or assent, an interval history, physical examination, echocardiogram, and completion of patient questionnaires for family history and their understanding of RF. The interval history included whether any recurrence had occurred and whether the patient had remained on antimicrobial prophylaxis. For those who stated that they were continuing penicillin prophylaxis, a urinalysis was done to detect the presence of penicillin.¹⁹

Statistical Methods

A Pearson *r* correlation analysis was performed by Dr Charles Hoff, University of Utah School of Medicine, Department of Pediatrics, to assess the relationship between percentage of isolates showing mucoid strains of group A streptococci and the number of RF cases.

RESULTS

Percentage of Mucoid Isolates

A tabulation of the percentage of mucoid isolates is shown in Table 1. Of 90 saved isolates collected before 1984, none was mucoid, but in 1984, 7.2% of the saved isolates were mucoid. This jumped dramatically in 1985 to 21.2%, subsequently falling to 8.2% in 1986 and down to 2.9% in 1987. Mucoid isolates persisted at lower percentages (between 0.5% and 4%) except for 1993, when there was a single mucoid isolate encountered in only 8 *S pyogenes* isolates stored that year. In 1996, the percentage of mucoid isolates rose to 10%. In 1997, the percentage climbed to 14.6%, and in 1998, the percentage reached a high of 18.3%. These isolates all came from patients at PCMC or from throat swabs referred by community physicians until the summer of 1998, when a surveillance program was initiated whereby all streptococcal isolates from the surrounding Intermountain Health Care Laboratories were sent to PCMC. Thus, the later months of 1998 through 2001 represent a wider sampling of the entire state and not just at PCMC. With this wider sampling, the percentage of mucoid strains dropped to 10.6% for the late months of 1998, to 3.3% in 1999, 1.6% in 2000, and 0.9% in 2001.

Cases of RF

All patients satisfied the revised (1985) or updated (1992) Jones criteria. Only minor variations in the frequency of major manifestations were observed.

Figure 1 graphically demonstrates how the in-

TABLE 1. Group A, β -Hemolytic Streptococci From PCMC

Year	Frozen Isolates			
	Cases of RF	No. of Isolates	No. of Mucoid Isolates	% of Mucoid Isolates
1983	3	90	0.0	0.0
1984	10	152	11	7.2
1985	61	453	96	21.2
1986	41	255	21	8.2
1987	34	946	27	2.9
1988	29	972	14	1.4
1989	34	1034	14	1.4
1990	39	1103	11	1.0
1991	24	510	10	2.0
1992	22	385	2	0.5
1993	28	8	1	12.5
1994	24	35	2	5.7
1995	19	26	0	0.0
1996	26	40	4	10.0
1997	41	48	7	14.6
1998	78	191	35	18.3
1998		1173	124	10.6
1999	31	3561	118	3.3
2000	35	2723	43	1.6
2001	16	1580	15	0.9

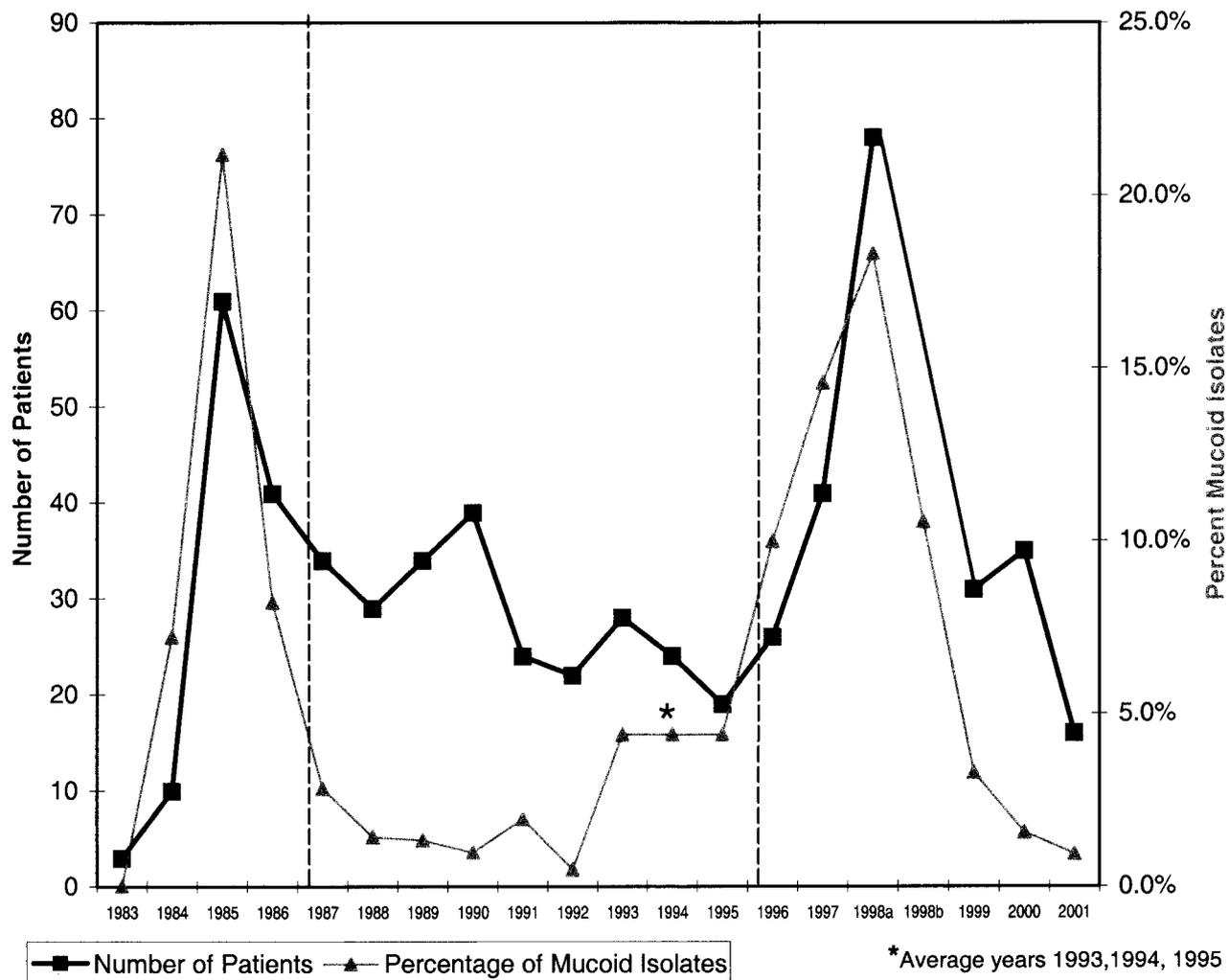


Fig 1. The number of cases of RF encountered yearly is shown by (■) along with the percentage of mucoid strains is shown by (▲). Only 8 isolates were stored in 1993, and 1 was mucoid. In 1994, only 35 isolates were stored, and 2 were mucoid. In 1995, 26 isolates were stored, but none was mucoid. Because of the small numbers of isolates stored during 1993–1995, these years were averaged*, ie, 69 isolates/3 mucoid (4%).

creased percentage of mucoid strains parallel the increased number of cases of RF during the initial years of the resurgence and the second peak 12 to 13 years later. In the intervening years, mucoid strains persisted at a lower percentage during the time that cases of RF were encountered less frequently, although at yearly rates ~6 times higher than in the decade before 1985. The relationship between numbers of RF cases and percentage of mucoid strains of group A isolates for all years included is positive and statistically significant ($P < .01$)

Patient Age

In the years 1985 and 1986, the median age of the patients with RF was 10 years, with a mean of 9.70 years, a range of 3 to 16 years, and a standard deviation of 4.04 years. In 1997 and 1998, the median age was 11 years and the mean age was 11 years, with a range of 5 to 19 years and standard deviation of 4.21 years. Of the 41 patients who acquired RF in 1997, all but 3 children would have been <5 years in 1986. Of the 78 patients who acquired RF in 1998, 1 would have been 3 years of age, 2 would have been age 4, and 1 would have been age 5 in 1986. All others

would have been >5 years. Thus, of the 119 patients who acquired RF in 1997 and 1998, 114 (96%) would have been 4 years of age or younger during the initial 2 years of the resurgence.

Follow-up of 1985–1986 Patients

Of the 61 patients who presented in 1985, 28 (46%) were reevaluated in 1999 and 2000. Of this group, 3 (11%) individuals had experienced a recurrence; 2 occurred in 1987, and 1 occurred in 1994. Of the 41 patients who had acquired RF in 1986, 16 (39%) were seen for follow-up. Three (18%) had experienced single recurrences all before 1990. Of the 44 reevaluated patients who had RF in 1985 and 1986, none had a recurrence during the exacerbation in 1997 and 1998. Only 10 of these 44 professed maintaining oral penicillin prophylaxis. Of these 10 patients, only 7 had urine checked for penicillin and only 3 of 7 tested had detectable penicillin. Thus, it is likely that <10% had maintained adequate prophylaxis and yet none experienced a recurrence during the 1997–1998 exacerbation of RF. This offers strong support that the 1985–1986 patients had immunity to the organism(s) responsible for the 1997–1998 exacerbation.

In 1986, only 1 patient with acute RF had a positive throat culture at PCMC. As previously reported, this isolate was inadvertently discarded. In 1998, there was a single positive culture, from a patient with RF, that was mucoid and later was typed as M-18 by the LHBP. The explanation for the low recovery rate of *S pyogenes* from RF patients is attributable to the manner in which the patients were referred to PCMC. All patients were referred by private physicians with at least a tentative diagnosis of RF and were routinely given an injection of penicillin or started on oral antibiotics by the referring physicians. Throat cultures were obtained at PCMC only when the patient was seen within 24 hours after starting antibiotics. Sporadic attempts at recovery of positive cultures from the offices of referring physicians were routinely unsuccessful because they typically had been discarded.

Isolates from microbiology laboratories, school surveys, and siblings were sent to the WHO Reference Lab University in Minnesota during 1986. Six group A streptococcal isolates were obtained from 6 siblings of 4 RF patients. The 5 mucoid strains included 1 M-type 18, 3 M-type 3, and 1 M-type 1. Of the 27 isolates obtained from the microbiology laboratory at PCMC and University of Utah, 13 were mucoid and were typable. These include 1 of M-type 1, 2 of M-type 3, and 10 of M-type 18. From 100 asymptomatic school children who were randomly selected and had throat cultures taken in Roosevelt, Utah, a community of 3500 in which 9 cases of RF had been confirmed, 15 had positive cultures. Eight of the 15 were mucoid, and all were M-type 18. Of the 33 isolates that were M-typable in 1986, 26 were mucoid. Nineteen (73%) of the M-typable isolates were M-18, 5 (19%) were M-type 3, and 2 (8%) M-type 1. In 1998, the WHO Reference Lab serotyped 103 isolates. Fifty-one were mucoid. Forty-four of the mucoid isolates were M-type 18 (86%), 1 (2%) was M-type 3, and 6 (12%) were other types (1, 4, 6, 10, 12, and nontypable).

The molecular analysis of M-18 organisms conducted at LHBP has been reported.²⁰ This extensive study showed a restricted genetic variation in isolates from the initial outbreak (1985–1986) and the exacerbation (1997–1998).

DISCUSSION

The resurgence of RF in the Intermountain area surrounding Salt Lake City, Utah, during the last decade and a half of the 20th century and extending into the 21st century represents the largest number of documented cases that have occurred in the United States in the past 50 years. The purpose of this report is to note the temporal association of the highest incidence of this resurgence of RF cases with an increased presence of mucoid strains of *S pyogenes* in the community. Although the relationship of mucoid strains to the highest incidence of RF in this civilian population is temporal, the coincidence is not unlike the past experience in the military, in which heavily encapsulated mucoid strains were considered to be responsible for near epidemic outbreaks of RF.²¹ The past experience in the United States has led to the

well-accepted concept introduced by Stollerman²² and others²³ that only a limited number of M-types (eg, 1, 3, 5, 6, 18, 24) are rheumatogenic. The demonstration that those strains that primarily cause pharyngitis and RF (class 1) have a different M-protein molecular structure from those strains that primarily cause skin infections and glomerulonephritis (class 2) supports the concept of rheumatogenic strains.²⁴ Our recent experience offers additional support that a limited number of M types are rheumatogenic and often are mucoid. Although M-18 was dominant, it was not the exclusive M type that was mucoid in the community.

The capsule is known to be a virulence factor that resists phagocytosis²⁵ but has not been considered to have a significant additional role in the pathogenesis of RF or the valve damage leading to rheumatic heart disease. Attempts to explain the pathogenesis of RF and rheumatic heart disease have been most strongly focused on the molecular mimicry of M-protein polypeptides to myosin and tropomyosin^{26,27} and group A carbohydrate to valvular tissue.²⁸ The mechanism, however, remains incompletely defined. One could question whether and how the capsule of mucoid strains potentiates the rheumatogenic capability of M-proteins or whether the capsule itself could be an independent factor in causing RF. Studies conducted at the LHBP did not detect any mutation in the *covR* or *covS* genes that control capsule formation in the M-18 isolates from Salt Lake City.¹⁹

An experience similar to ours occurred in Kansas City, Missouri, during 1987, when 37 of 1700 positive group A streptococcal cultures were noted to be highly mucoid.²⁷ The mucoid strains represented only 2% of the total positive cohort, and none acquired RF. However, 14 cases of RF were diagnosed in Kansas City, Missouri, in that same year (1987), whereas only 5 cases of RF had been encountered in the previous 5 years. Their report did not state what had been their experience with mucoid strains before 1987.

The ages of the patients involved in the 1997–1998 exacerbation of the resurgence clearly suggests that these patients represented a new group of susceptible individuals because they either were not yet born or were so young in 1985 and 1986 that they likely would not have acquired RF. The patients who acquired RF in 1985–1986 experienced a total of 6 recurrences before 1994 but did not have a recurrence in 1997–1998, although most were not maintaining secondary prophylaxis. It should be noted that discontinuance of prophylaxis in all cases was by patient decision and not physician directed.

The high percentage of mucoid strains associated with the largest number of cases of RF is impressive. During the intervening years between the 2 periods of highest incidence, cases of RF were still seen at a rate 5 to 6 times higher than the decade before 1985. During this intervening period between 1987 and 1997, mucoid strains were still present in the community. We do not know what the usual prevalence of mucoid strains may be because we have no background data in our own community and do not know of any reported prevalence of mucoid strains.

The reported incidence of mucoid cultures in Kansas City in 1987 was considered unusual. Most of the time during the lower incidence of the resurgence, mucoid strains were present at levels >2% (Fig 1). Although we have no other explanation for the persistence of the resurgence of RF in our community, we appreciate that our enthusiasm must be tempered because we do not have absolute proof that these mucoid strains were responsible for the individual cases of RF. What we describe is only a temporal association.

CONCLUSION

A clear-cut temporal association with the highest incidence of RF during the resurgence of RF in the Intermountain area was clearly associated with an increase of mucoid strains of *S pyogenes* in the community.

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