Natural history of impetigo: *I. Site sequence of acquisition and familial patterns of spread of cutaneous streptococci*

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Distribution of positive normal skin sites among wrist, ankle, and back was similar (28-37%) although 62% of lesions were on the legs. Recovery of a serotype from normal skin was associated with a high risk (76%) of subsequent development of lesions due to that type.

New streptococcal serotypes usually entered a family during the peak or decline of a preceding serotoype with a tendency of one to predominate. Among family members the mean interval from index to secondary skin acquisition of streptococci was 4.8 days, but 21 days elapsed from first appearance to last acquisition of skin disease.

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Natural History of Impetigo

I. SITE SEQUENCE OF ACQUISITION AND FAMILIAL PATTERNS OF SPREAD OF CUTANEOUS STREPTOCOCCI

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ABSTRACT The appearance on and spread of Group A streptococci among different body sites in relationship to the development of impetigo were studied prospectively in 31 children in five families. During July and August 1969 intensive clinical, bacteriological, and serological observations were made, including cultures taken at least every other day.

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New streptococcal serotypes usually entered a family during the peak or decline of a preceding serotoype with a tendency of one to predominate. Among family members the mean interval from index to secondary skin acquisition of streptococci was 4.8 days, but 21 days elapsed from first appearance to last acquisition of skin disease.

In the population as a whole, streptococci were recovered in high frequency from normal skin before the increase in prevalence of lesions and also later in the fall when cutaneous infections were absent.

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INTRODUCTION

Studies from a number of centers in recent years have revealed that Group A streptococci, usually of certain serological types, are commonly associated with impetigo and that skin infections with some of these types may lead to acute glomerulonephritis (1–5).

However, there are still many unanswered questions relating to the epidemiology and pathogenesis of streptococcal skin infections (6). Of paramount interest are the source(s) of the streptococci which cause skin infections, factors which contribute to and facilitate the development of cutaneous lesions, the modes by which streptococci spread within families and from site to site in an individual, and the effect of penicillin on acquisition of streptococci on the skin.

Streptococcal pyoderma has been an endemic problem at the Red Lake Indian Reservation in northern Minnesota for at least 20 years. Two well-documented outbreaks of acute glomerulonephritis associated with streptococcal M-type 49 skin infections occurred there in 1953 (7) and 1966 (5) and sporadic cases of pyoderma nephritis continue to occur (8). Group A streptococcal serotypes which were associated with skin lesions during the summer months were often found in the respiratory tract in the fall, a finding of Anthony, Kaplan, Chapman, Quie, and Wannamaker (5) which was confirmed in studies in Tennessee (9) and Alabama (H. C. Dillon, personal communication). Later studies in 1968 at Red Lake suggested that Group A streptococci were commonly isolated from the normal skin of children, and that

skin lesions frequently developed later in such children (10).

Therefore, during the summer and early fall of 1969 a prospective study was conducted at the Red Lake Indian Reservation to document more precisely the appearance and sequential spread of Group A streptococci among different body sites within the same individual and the relationship of these events to the development of impetigo. In addition, it was possible to elucidate patterns of introduction into and spread among family members of various streptococcal serotypes and to make observations on the reisolation of streptococci on normal skin and recurrence of skin lesions after penicillin treatment. Studies of the bacterial agents commonly associated with impetigo and their interaction in serially cultured lesions are presented in a separate communication (11).

METHODS

Beginning July 1 and continuing through August 1969, 37 children between the ages of 1 and 15 yr from six families living at the Red Lake Indian Reservation were examined daily except Saturday and Sunday. All the children in this age group in any single family were included. Routine cultures of the nose, throat, and normal skin sites (wrist, ankle, back) were obtained three times weekly. When skin lesions were present, repeated cultures of one or more lesions were taken, at least three times a week and often daily. Urine was tested once weekly for hematuria and proteinuria by the "Hemacombistix" method (Ames Co., Inc., Elkhart, Ind.). Blood specimens were obtained at the initiation of the study and at 4 and 8 wk. After these 2 months of intensive observations, the children were reexamined and cultures were taken on September 3, 10, 17, and October 1. A majority of the children were also examined and cultured on November 5. Written parental consent was obtained for each child in the study.

Cultures were obtained on home visits and swabbed immediately on 6% sheep-blood trypticase-soy agar plates containing 1% Todd-Hewitt broth and incubated overnight at 37°C. The plates were examined at 18 hr, left at room temperature and reexamined on the 2nd and 3rd day. Dry cotton swabs were used to obtain cultures from the throat (posterior pharynx and tonsillar areas) and nose (anterior nares). Cotton-tip applicators moistened with Todd-Hewitt broth were used to swab 4 × 4 cm areas of the volar aspect of the wrist, the ankle above the medial malleolus, and the mid-back. Skin lesions were cultured by cleansing with 70% alcohol, lifting the crust with a sterile 20 gauge needle, and touching the base or lesion fluid with a cotton-tip applicator.

Three colonies of beta hemolytic streptococci from each positive culture were transferred separately to Todd-Hewitt blood broth, grown overnight at 37°C, and frozen for grouping and typing. All Group A isolates were further identified by T-protein agglutination patterns and M-protein precipitation reactions.[1] Sera for grouping, M-typing, and T-agglutination were obtained from the Center for Disease Control, Atlanta, Ga. Other antisera were provided by Dr. Rebecca Lancefield of The Rockefeller University, New York, and by the Central Public Health Laboratory at Colindale, England, through the courtesy of Dr. W. R. Maxted and Dr. M. T. Parker.

Four streptococcal antibody determinations were performed on the sera. Antistreptolysin O (ASO),[2] antideoxyribonuclease B (anti-DNase B), and anti-nicotinamide adenine dinucleotidase (anti-NADase) titers were measured, as described in previous publications (12–15). Streptococcal Group A carbohydrate antibodies were determined by the radioimmune precipitation technique of Halpern and Goldstein (16) as modified by Dudding and Ayoub (17).

RESULTS

Prevalence and serotypes of streptococci. From July 1 to October 1, 1969, there were 4021 cultures taken from 31 children distributed among the five families included in this analysis.[3] 34% of these cultures were positive for Group A streptococci. Table I summarizes the number of cultures taken from each site and the percentage positive at each site for Group A streptococci. Cultures of the normal skin, regardless of site, were about three times more likely to be positive for Group A streptococci than those of the nose or throat. Group A streptococci were isolated from a high percentage of lesions, usually in large numbers (50 or greater colonies per plate).[4] Quantitation of Group A streptococci recovered from normal body sites (normal skin, nose, and throat) revealed similarities and differences among

TABLE I

Prevalence of Group A Streptococci at Different Culture Sites

Site	No. cultures taken	No. positive for group A streptococci	Per cent
Nose	656	72	11
Throat	656	64	10
Normal skin (wrist, ankle, back)	1989	624	31
Skin lesions	720	617	86
	4021	1377	34

[1] Specific M-antisera available were: 1–6, 8, 9, 11–15, 17–19, 22–33, 36–44, 46–49, and 51–57.

[2] *Abbreviations used in this paper:* anti-DNase B, antideoxyribonuclease B; anti-NADase, anti-nicotinamide adenine dinucleotidase; ASO, antistreptolysin; CFU, colony-forming units.

[3] One family of six children had so few streptococcal isolates that analysis of spread among different body sites or among different family members was not feasible. This family was therefore omitted from the analysis reported here but is included in the subsequent report (11) dealing with staphylococci as well as streptococci. Furthermore, culture results for all the families from the November 5 visit were omitted because there were few streptococcal isolates recovered and no lesions were present.

[4] Other groups of streptococci were not commonly isolated from lesions: Group G in four instances, Groups B and C in none.

TABLE II

Quantitation of Group A Streptococci Recovered from Normal Body Sites

Positive cultures		Number of colonies per plate (per cent distribution)		
Site	Number	1–9	10–49	50 or greater
Nose	72	40	40	20
Throat	64	52	27	21
Normal skin	624	57	33	10

these sites (Table II). The percentage of positive nose cultures with 10 or more colony-forming units (CFU) per primary culture plate was higher (60%) than that for normal skin cultures (43%) or for throat cultures (48%).

Table III lists the six streptococcal serotypes isolated from the five families during the study period, their frequency of recovery among all cultures taken and their per cent distribution among all Group A streptococci recovered. M-57, the major type, accounting for 50% of total Group A streptococci recovered and for 17% of all cultures taken, was associated with acute nephritis in two children in the study (8). Skin lesions due to M-type 57 occurred in 15 other children in the study, but without associated nephritis. The other five streptococcal serotypes accounted for smaller percentages of positive cultures. Three of the five families had two streptococcal types, one family had four types, and one other family had only one type, M-57, recovered. 73% of all Group A streptococci isolated in this study were M-typable, which compares favorably with typability of pyoderma strains reported previously from studies at the Cass Lake and Red Lake Indian Reservation (18) as well as from other areas (2, 3, 9, 19, 20).

In Fig. 1 the percentages of children with positive cultures of Group A streptococci from the nose, throat, normal skin sites, and skin lesions are plotted for each week of the study. For the first 3 wk the frequencies of positive skin sites and lesions showed some fluctuation but were at comparable levels. The distinct upswing in prevalence of lesions lagged behind that for positive normal skin sites during late July and early August, and throughout the remainder of the study there was maintenance of a higher level of positive normal skin sites than lesions. The peak frequency of positive normal skin sites and skin lesions occurred during August 4–10, as did the frequency of positive nose cultures. The sharp increase in prevalence of positive nose cultures followed that for normal skin sites and lesions. The prevalence of positive throat cultures showed little fluctuation. There was a higher frequency of children with positive normal

TABLE III

Streptococcal Serotypes Recovered

Serological classification		Per cent of all cultures taken	Per cent of group A streptococci
T-pattern	M-type		
8/25/1–19	57	17	50
28	56	7	19
12	NT*	4	12
11	NT	2	8
6/15/17/23/47	NT	2	7
14/49	49	1	4

* Not M-typable with available antisera.

skin sites (one or more of three sites cultured) and of children with skin lesions than of children with positive respiratory tract cultures from the beginning of the study until the end of August. A rather sharp decline in skin lesions occurred at the beginning of September, but a high percentage of individuals with positive normal skin site cultures continued (range 47–68%) throughout September. On the final November 5 visit 20 children were cultured, four of whom (20%) had positive normal skin site cultures. No lesions were present at that time.

Distribution of lesions compared with positive normal skin sites. In Fig. 2 is contrasted the per cent distribution of positive normal skin cultures and skin lesions among different body sites. Although the percentage distribution of normal skin sites positive for Group A streptococci was generally similar among upper and

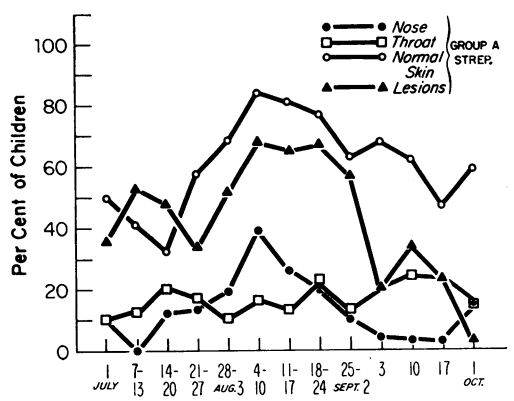

FIGURE 1 Per cent of children with positive cultures for Group A streptococci from the nose, throat, normal skin sites, and skin lesions for each week of the study. (Normal sites were considered positive if positive on any of three culture days during the week. Normal skin sites were considered positive if one or more of three sites cultured was positive. Lesions were cultured if present on any day and considered positive if Group A streptococci were recovered at any time during the week.)

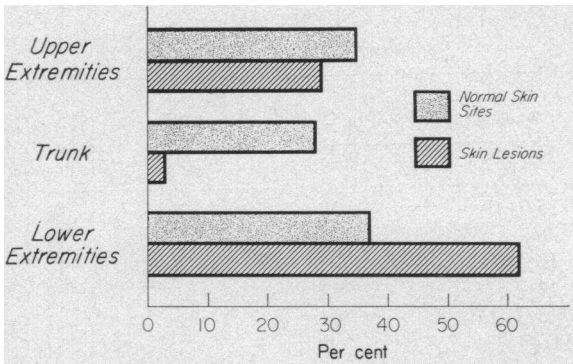

FIGURE 2 Per cent distribution by body site of positive cultures for Group A streptococci from normal skin and from skin lesions.

lower extremities and trunk, ranging from 28 to 37%, the lower extremities accounted for 62% of the total lesions harboring Group A streptococci. 29% of the Group A streptococcal lesions were on the upper extremities and only 3% on the trunk. Since the trunk and buttocks in addition to the extremities were examined on each visit, the paucity of lesions on the trunk cannot be explained by failure to detect them at a less exposed site.

Appearance of lesions in temporal relationship to positive cultures at other sites. All of the children developed skin lesions during the study period, and in 21 of the 31 children (68%) Group A streptococci of the same serotype were recovered from normal skin sites before the development of skin lesions.

The sequence in which streptococci of the same serotype were recovered from various body sites was examined more closely by analyzing episodes in individual children. Criteria were established to insure that sufficient information was available for valid analysis. The first appearance of the organism at each site was documented and considered valid for analysis if the child was seen and cultured on at least four visits during the preceding 2 wk. Table IV presents the sequence of streptococcal recovery among the cultured sites. Among the 31 children there were 42 episodes of lesions of different serotypes which could be analyzed by the above criteria in relation to recovery of streptococci from normal skin. In 31 of these 42 episodes (74%) streptococci of the same serological type were recovered first from normal skin. These 31 episodes occurred in 21 children (13 children had one episode, six children had two episodes each, and two children had three episodes) and represented occurrences of lesions of different serotypes except for 4 episodes (in four children) which were recurrent episodes due to the same streptococcal type. There were six episodes in which positive normal skin cultures coincided with appearance of lesions and in five positive normal skin cultures followed lesions. A variety of streptococcal serotypes was recovered in these episodes.

TABLE IV

*Site Sequence of Recovery of Group A Streptococci by Episodes in Individual Children**

Sequence	Frequency‡	Interval	
		Range	Mean
		days	
Normal skin prior to lesions	31/42 (74%)	2–33	10.3§
Normal skin prior to respiratory tract‖	31/32 (97%)	2–58	17.7§
Lesions prior to respiratory tract‖	23/31 (74%)	3–48	18.2

* Sequence analyzed for the same serological type.

‡ Number of episodes with this sequence (numerator) out of total number of analyzable episodes for these two sites (denominator).

§ The difference between the means of the first and second sequences (10.3 and 17.7) is significant. (Observed difference is 2.5 times the standard error.)

‖ Nose and/or throat.

Similarly, there were 32 episodes in which the appearance of streptococci in the nose and/or throat could be analyzed in relation to positive normal skin cultures. In 31 of these episodes (97%) from 24 children, streptococci of the same serological type appeared on normal skin before recovery from the respiratory tract. In 6 of the 31 children, streptococci of the serological type recovered from skin or lesions were never recovered from the nose or throat. In one episode from another child, streptococcal recovery from these sites coincided. No child had positive respiratory tract cultures before appearance of the organisms on the normal skin.

Recovery of streptococci from the respiratory tract also followed the appearance of lesions in 74% of the 31 analyzable episodes. These 23 episodes occurred in 19 children (15 children, one episode each; four children, two episodes each). In four of the other eight analyzable episodes, positive respiratory tract cultures coincided with and in four preceded the appearance of lesions.

Table IV also shows the ranges and means of the intervals between appearance for the sequences indicated. In contrast to the shorter interval between recovery of streptococci on normal skin and the development of lesions (mean 10.3 days) the appearance of streptococci in the nose and throat was delayed and followed recovery from the normal skin (17.7 days) and lesions (18.2 days).

Fig. 3 illustrates the distribution of the intervals of the recovery sequences listed in Table IV. There is little difference in the wide scatter of intervals for the recovery of streptococci from the normal skin or from lesions before recovery from the respiratory tract (2nd and 3rd panels). The median[5] intervals are 15 days for

[5] Because of the skewed distribution median values may be preferable instead of arithmetic means given in Table IV.

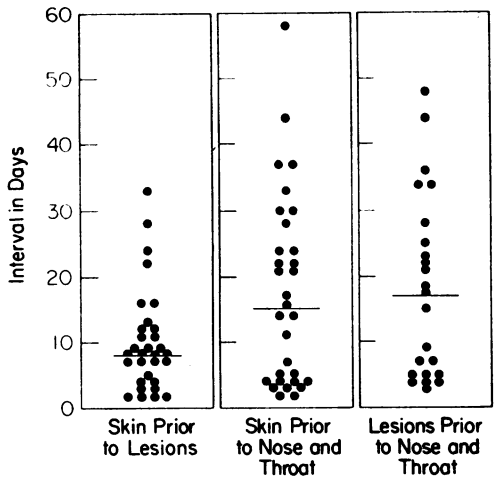

FIGURE 3 Scattergram comparing the intervals (days) between recovery of streptococci from various body sites (see text). The median intervals are shown by horizontal lines.

skin before nose and throat and 17 days for lesions before nose and throat. In contrast the intervals for skin before lesions (1st panel) show less widespread scatter with considerable clustering under 10 days (median value of 8 days).

There was a difference in intervals when the appearance of streptococci in the respiratory tract was analyzed separately for nose and throat. The mean interval between isolation of streptococci of the same serotype for the first time from the normal skin and later from the nose was 14 days and from normal skin to throat was 20 days. Analysis of the mean intervals between appearance in lesions and then in the nose or throat was similar (15 days and 20 days, respectively). In none of the children was there any clinical evidence of streptococcal respiratory disease during the study period.

TABLE V

Frequency of Development of Skin Lesions After Recovery of Serologically Related Streptococci from Normal Skin

Serological classification			Interval	
Group	M or T	Frequency*	Mean	Median
			days‡	
A	M–57	12/14	7.3	6.0
A	M–56	4/6	14.3	10.5
A	T–12§	6/8	11.2	7.0
A	Misc‖	6/9	14.3	12.5
G	—	4/14	8.3	8.5
B	—	0/5	—	—

* No. who developed lesions/No. with streptococci on normal skin.

‡ Between recovery from normal skin and development of lesions.

§ Not M-typable.

‖ T–11, T–6/15/17/23/47, and M–49.

Risk of lesions developing in children with positive normal skin cultures. The recovery of Group A streptococci from the normal skin of an individual was associated with a high risk of subsequent development of skin infection in that individual with a strain of the same M or T classification (Table V). 86% of the children with M-type 57 streptococci on the normal skin

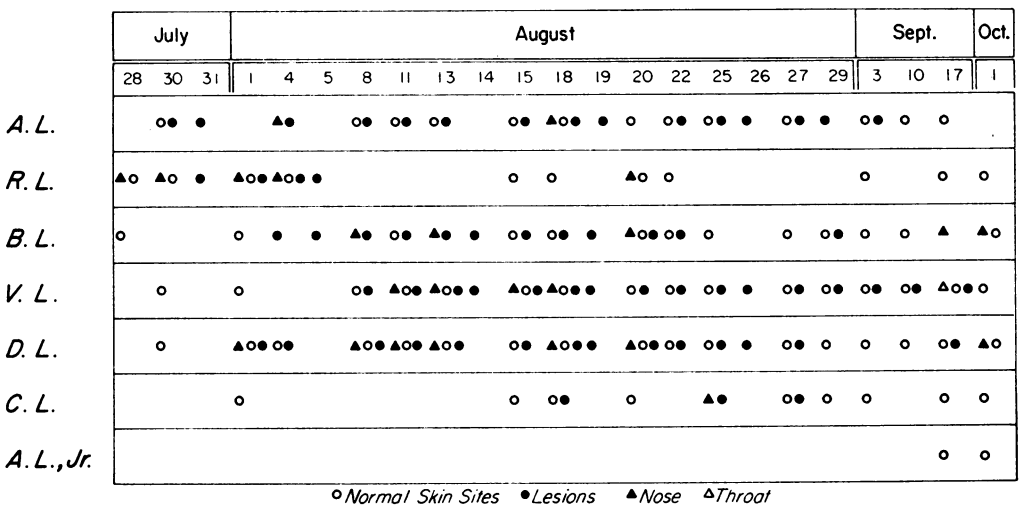

FIGURE 4 Site sequence of recovery of M-type 57 streptococci from various body sites among seven members of family 1 for each week of the study. Normal skin sites, lesions, nose, and throat are designated with symbols and each symbol represents one or more positive cultures for that culture date.

subsequently developed skin lesions with this type. The percentage who developed lesions after the appearance of other Group A serotypes on the skin varied from 67 to 75%. Only 4/14 of children with Group G streptococci on the normal skin and none of the small number of children with Group B streptococci on the skin developed lesions due to these groups. Among the Group A streptococci, the mean interval between recovery of streptococci from the skin and development of lesions was shortest with M-type 57 (7.3 days), and varied from 11.2 to 14.3 days for the other types. The mean interval from acquisition of Group G streptococci on the skin to development of lesions was 6.5 days.

Familial patterns of acquisition and spread of streptococci. Fig. 4 is an example of the site sequence of recovery of a single serotype (M-type 57) of streptococci among the children of one of the families (hereafter designated family 1) under intensive observation. The first appearance of M-type 57 in the family was on July 28, although three other serotypes were recovered from July 1 up to this time. In five of the seven children M-type 57 streptococci were isolated from the normal skin on one or two culture visits before the development of skin lesions with this type (mean interval of 7.6 days). In A. L., Jr., there was recovery of M-type 57 streptococci on the normal skin late in the study but no lesions due to this type developed during the period of observation. As expected, streptococci continued to be isolated from normal skin sites after the appearance of lesions. Of interest is the observation that three children, R. L., B. L., and C. L., persisted with the strain on normal skin from late August or early September until the end of the study during which time they had no skin lesions.

In this family, positive respiratory tract cultures were limited almost exclusively to the nose. In five of six children the first appearance of a positive nose culture followed the appearance of the strain on normal skin and in four of six also followed occurrence of skin lesions, suggesting transmission from skin to nose. With one exception (patient V. L., on September 17), positive throat cultures were conspicuously absent.

TABLE VI

Spread of Group A Streptococci within the Families

	Interval	Mean
	*days**	*days*
Index skin acquisition to secondary skin acquisition‡	[2, 2, 2][3][3] [4, 4][7, 7, 7][12]	4.8
Index skin infection to last skin infection	[1][13][15][19] [37][41]	21.0

* Each bracket includes figures from analysis of one serotype in a family and multiple figures within a bracket designate the intervals of children with simultaneous secondary skin acquisition.

‡ Skin acquisition as defined in this analysis means recovery of streptococci from normal skin and/or lesions.

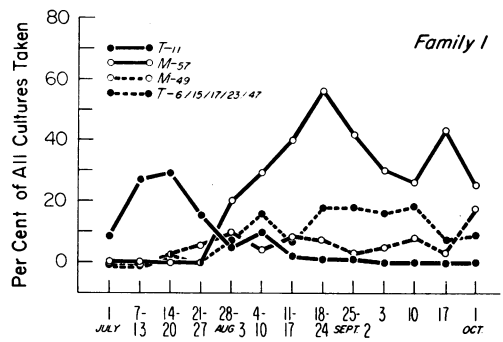

FIGURE 5 Percentage of all cultures taken positive for four different streptococcal serotypes recovered from family 1 by week of study.

No evidence of nephritis occurred in this family during the intensive study period or at long-term follow-up, despite widespread dissemination within the family of a known nephritogenic strain which was associated with nephritis in other families.

Findings similar to these were not confined to one streptococcal serotype or to one family; the other streptococcal types common to the five families behaved in a similar fashion in their site sequence of spread and spread within the family (see below).

Intervals between acquisitions and infections within families. In family 1 (see Fig. 4) the initial (index) acquisition of M-type 57 streptococci was in R. L. and B. L. (on July 28), and in 2 days there was secondary acquisition of this strain by three other family members. There was an interval of 19 days between the appearance of the index infection (skin lesions) and the development of skin infection in the last of the six children in this family who had lesions due to this streptococcal type.

Table VI gives the intervals between an index acquisition (normal skin and/or lesions) of a streptococcal serotype by a family member(s) and the first secondary acquisition (normal skin and/or lesions) by another family member(s). There were six streptococcal serotypes which appeared initially in the five families while they were under observation (one each in four families; two in another family). A range of 2–12 days (mean 4.8) was found between index and secondary skin acquisition of streptococci in the families. The mean interval between the first (index) and the last appearance in family members of cutaneous infection with the same streptococcal serotype was 21 days.

Chronology of strain movements within families. Since four of the five families had more than one strep-

tococcal serotype isolated during the study period, this offered an opportunity to examine the chronology of strain movements in these families. Fig. 5 illustrates the chronology of strain movements into family 1 in whom four different serotypes were isolated. The movements of the major type, M-57, among various body sites of individual family members was previously presented in Fig. 4. Two of the strains, classified as T-11 and T-6/15/17/23/47 by T-agglutination, could not be M-typed in our laboratories. In this family only T-11 was isolated during the first 2 wk of the study; recovery of this serotype then declined. The M-type 49 and T-6/15/17/23/47 serotypes first appeared on July 14, but they never gained ascendancy. M-type 57 reached a peak frequency of 57% of all cultures taken from August 18 to 24 and continued as the predominant strain through October 1. During the week of August 18–24, 83% of all cultures taken were positive and all four streptococcal types were represented.

In Fig. 6 is plotted the change in strains for two families in whom two serologically different strains were recovered, M-type 56 and T-pattern 12 (which was not M-typable). There were 12 children in these two families, living quite close to each other and sharing many facilities and activities, so they may be considered essentially as one extended family unit. From these two figures (5 and 6) we see that new serotypes may enter a family during the peak or decline of a preceding serotype, and that they may coexist for periods of time, with a tendency for one to become predominant.

Streptococcal antibodies. Among the four streptococcal antibody determinations performed on serial bleedings from the 31 children, there were differences in the percentage of children who developed significant antibody

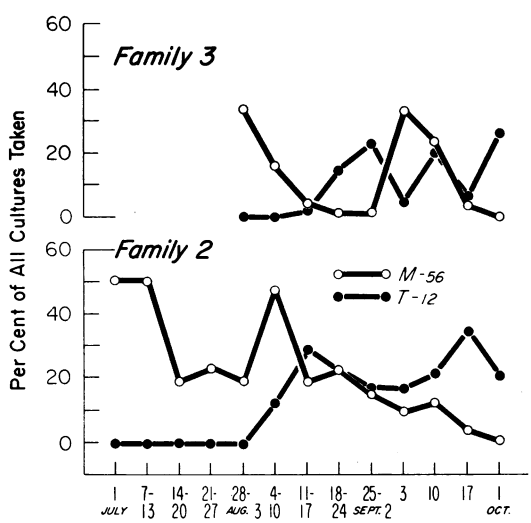

FIGURE 6 Percentage of all cultures taken positive for streptococcal types M-56 (open circles) and T-12 (closed circles) recovered from families 2 and 3 by week of study.

TABLE VII
Streptococcal Antibody Rises and Initial Mean Titers Among the 31 Children

Antibody	Children with rise* No.	Per cent	Initial mean value in children with‡ Rise	No rise
ASO	6	19	88	251
Anti-DNase B	13	42	381	624
Anti-NADase	11	36	101	245
Anti-group A carbohydrate	8	26	0.35	0.74
One or more of above	18	58		

* For ASO, anti-DNase B, anti-NADase, 0.2 log rise or greater. For anti-group A carbohydrate, 10% or greater increase in fraction of antigen precipitated. (If 5% or greater is taken as significant, four additional children developed an antibody response to the antigen.)

‡ For ASO, anti-DNase B, anti-NADase geometric mean titers are given; for anti-group A carbohydrate the arithmetic mean.

rises to the different streptococcal antigens (Table VII). The anti-DNase B response appeared to be the best indicator of streptococcal skin infection. Few children developed an ASO rise. Only 26% revealed an increase in group A carbohydrate antibody level, but the initial antibody levels were generally high. Six of the eight children with a Group A carbohydrate antibody rise were less than 4 yr of age, and had lower initial titers, reflecting most likely fewer previous experiences with streptococcal disease. The initial geometric mean titers were higher for all four antibodies in children who developed no rise compared with those who did demonstrate a rise.

Effect of treatment on persistence or reacquisition of streptococci and reinfection. It was possible to make a few observations on the relationship of treatment administered in the hospital to the persistence or subsequent reappearance of streptococci of the same serotype on the normal skin and on recurrence of skin lesions due to the same type. Five children from the study group were hospitalized and received various treatment regimens as shown in Table VIII. No antibiotic was given on discharge from hospital. No skin lesions were present on discharge, but all of the children had streptococci recovered from normal skin sites after completion of antibiotic treatment, and the majority were positive on two or more occasions. Intervals between the last day of treatment and the first recovery of streptococci from normal skin ranged from less than 1 day to 10 days. Since all of the children were not cultured while in the hospital, it is not certain if streptococci persisted on the normal skin while on treat-

TABLE VIII

Relationship of Treatment in Hospital to Persistence or Reacquisition of the Same Serotype and to Reinfection with this Type

Patient	Treatment	Interval between last dose or injection and recovery of streptococci on normal skin	Recurrence of skin lesions
		days	
D. B.	Benzathine penicillin*	8	No
A. B.	Benzathine penicillin*	10	No
D. R.	Aq. pencillin i.m., 8 doses Oral penicillin, 7 days	4	Yes‡
L. L.§	Aq. penicillin i. m., 6 doses Oral penicillin, 7 days	<1‖	No
L. L.§	Oral penicillin, 7 days	<1‖	Yes‡

* 600,000 U.
‡ Same serotype as before treatment.
§ Details of clinical history reported previously (8).
‖ Skin culture positive day of discharge from hospital.

ment or were reacquired. In the two children treated with Bicillin (Wyeth Laboratories, Philadelphia, Pa.) no further skin lesions occurred, whereas two of the other three children developed lesions after recovery of streptococci from normal skin (15 and 23 days after the end of treatment). The streptococcal serotype cultured from these lesions was the same as that recovered from lesions before treatment.

DISCUSSION

It has been recorded that streptococcal impetigo usually occurs in the absence of overt streptococcal disease of the respiratory tract (1, 21). However, without frequent observations during the period before the development of impetigo, the possibility of previous infection, particularly subclinical or mild infection, of the respiratory tract could not be excluded. Therefore, it has not been clear whether Group A streptococci in the nose or throat play any significant role as a reservoir in the acquisition and spread of skin infections. The results of the present study, based on intensive serial observations in individual children, initiated in many cases some weeks or months before the appearance of skin lesions, clearly eliminate the upper respiratory tract as a source of infection of the skin. In 94% of instances the streptococcal strain was recovered from the normal skin of an individual before it appeared in the respiratory tract and in 74% of instances lesions harboring this specific strain developed before the strain appeared in the upper respiratory tract.

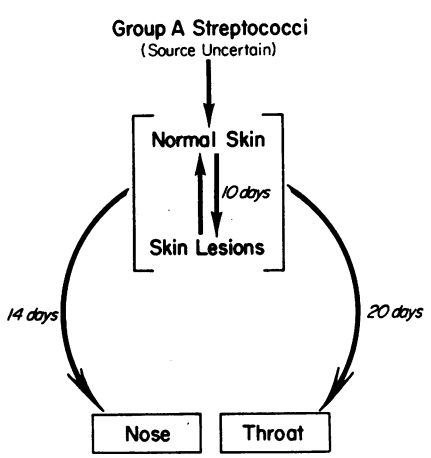

FIGURE 7 Concept of the sequence of spread of Group A streptococci among different body sites based on the findings of this study.

Studies carried out at the Red Lake Indian Reservation in 1968 revealed that a primary factor in the development of pyoderma was previous acquisition of streptococci on the normal skin (10). The present study confirms these findings with observations at more frequent intervals and extends them to include several other pyoderma strains, including a serotype (M-57) with nephritogenic properties. Moreover, the risk of developing impetigo after the recovery of Group A streptococci from the normal skin is shown to be extraordinarily high (76%).

Traditionally, it has been thought that beta hemolytic streptococci are only rarely included among the normal skin flora (22), and that these organisms do not survive when artificially inoculated on normal skin (23). In addition, in vitro studies have shown that unsaturated fatty acids extracted from normal human skin are bactericidal for streptococci (24). The present study with intensive daily observations and culture surveillance (three times weekly) gives more credibility to the frequent recovery of streptococci from normal skin in certain populations, particularly those at high risk of developing pyoderma. Though only semiquantitative techniques were used, 43% of the positive normal skin cultures had more than 10 streptococcal CFU recovered from the small areas cultured. Other studies from this laboratory studying a similar group of children have revealed that if multiple sites of the forearm are cultured, streptococci are commonly recovered from more than one site.[6] Thus, the possibility that the presented observations are chance sampling events becomes less likely.

In Fig. 7 is presented our concept of the sequence of spread of Group A streptococci among different body sites of an individual based on the present study. Group A streptococci, from uncertain sources, contaminate

[6] Ferrieri, P., A. S. Dajani, and L. W. Wannamaker. Unpublished observations.

and possibly colonize the normal skin. After an insult(s) to the integrity of the skin such as insect bites, poison ivy, abrasions, or even undetectable trauma, skin lesions may appear if streptococci are present on the normal skin. The mean interval between appearance of streptococci on the normal skin and the development of skin lesions with the same serological type is 10 days. Often streptococci of the same serological type are recovered repeatedly from the normal skin during the interval before the development of lesions harboring this type. These findings are consistent with three possibilities: (*a*) repeated deposition on the normal skin; (*b*) survival for protracted periods (days) on the normal skin; (*c*) multiplication (colonization) on the normal skin. Unfortunately, it is not possible to determine which one(s) of the possibilities is (are) likely to be correct from the studies presented here.

The appearance of streptococci in the nose or throat of the individual is further delayed (more so for the throat). Respiratory tract acquisition almost always follows skin acquisition of streptococci (intervals of 14–20 days for nose and throat, respectively) and usually does not occur until after the development of skin lesions, suggesting transmission from normal or infected cutaneous sites. Respiratory tract acquisition of streptococci was often quite transient and did not result in clinical disease.

In the population as a whole, the low rather constant pattern of positive throat cultures throughout the study is in contrast to the fluctuation in positive nose cultures. The upswing in positive nose cultures which follows the sharp increases in prevalence of positive normal skin and lesion cultures may be due to contamination of the nose by streptococci from cutaneous sites. In this study the streptococcal serotypes recovered from the nose or throat did not differ from those recovered from normal skin and lesions.

Once skin lesions are established it seems reasonable that shedding of streptococci occurs, perhaps in large numbers, which can result in endogenous contamination of normal skin and also act as a source of spread for the acquisition of organisms on the skin of family members living and sleeping in close quarters. It is possible that streptococcal acquisition may result from cross-transmission within families or from other contacts.

It appears that within a relatively short period of initial acquisition of a streptococcal strain on the normal skin or in skin lesions by a family member(s), secondary acquisition by another member(s) takes place. This mean interval of 4.8 days contrasts with the longer interval of 15 days observed between index and secondary acquisition of streptococci in the throat of family members under prolonged observation in the Cleveland study (25). This difference may be in part artifactual, however, since in this latter study cultures were ordinarily obtained at only weekly intervals.

The shorter intervals for secondary family spread of cutaneous streptococci compared with streptococci from the throat are not readily explained but may be a reflection (in the case of the former) of: (*a*) more crowded living quarters in our families with greater opportunity for intimate physical contact and transmission of organisms; (*b*) possibly shedding of larger numbers of organisms from the normal skin or multiple skin lesions thus increasing the chance of secondary spread; (*c*) undefined biological differences of skin streptococci which may enhance survival and viability during transmission.

In our families a mean interval of 21 days elapsed between the first occurrence of skin infection and the last acquisition of skin disease (due to the same streptococcal serotype) by a family member. No comparable data are available from the Cleveland study.

The high frequency of positive normal skin site cultures during the last 4 wk of this study—at a time when skin lesions were declining or not present at all in most children—is intriguing. The serotypes recovered were those previously isolated from normal skin and from lesions. One speculation for this disparity is that type-specific antibodies may have developed to those types and prevented new lesions but not acquisition or persistence of streptococci on the normal skin. We have no data to support this theory, and little is known about the regularity with which such antibodies develop after skin infections or whether they can protect against reinfection of the skin (6). Other possibilities include the decline or disappearance of factors which may breech the integrity of the skin, such as insect bites and other trauma. Another possible factor is the routine weekly showering in school which could have affected the development of lesions in the school-age children after September 3.

The recovery of Group A streptococci from normal skin before development of lesions and later in the fall when no skin infections were present suggests frequent contamination of this body site from some environmental source with possibly survival on or even colonization of the normal skin. Whether these pyoderma strains possess unique biological properties which permit such phenomena is unclear.

The length of persistence or survival of streptococci on the normal skin has not been studied under controlled conditions but many children had the organisms recovered on two or more culture visits (separated by 2 or 3 days) before developing skin lesions. It also appears that streptococci can persist or be acquired on

the normal skin in spite of penicillin therapy. The five hospitalized children who received various regimens of penicillin had persistence or reacquisition of streptococci on the skin after treatment, with two developing lesions of the original serotype. The numbers are small but the suggestions from these data are that intramuscular benzathine penicillin may not interfere with the persistence or reacquisition of streptococci on normal skin, although it may prevent recurrence of skin lesions for a period of time. It appears that oral penicillin is less effective in preventing recurrence of lesions, a finding of other investigators in studies comparing different treatment regimens (26). A recent preliminary study of intramuscular benzathine penicillin as a prophylactic agent for skin infections has shown that streptococci can be recovered from the normal skin as early as 2 wk after administration of this long-acting penicillin (27).

Our finding that the percentage distribution of normal skin sites positive for streptococci was similar among the upper and lower extremities and back (28–37%) emphasizes that less exposed parts of the body (i.e., the back) can acquire the organisms. However, since 62% of the total lesions occurred on the legs, it appears that several factors, including trauma, may be etiologically important in the development of skin lesions. Duncan, McBride, and Knox (28) demonstrated in experimental production of streptococcal and staphylococcal skin infections in humans that there was a higher success rate of infecting the leg than the back or arm. Regional circulatory differences and possibly differences in oxygen and carbon dioxide tensions between the upper and lower extremities were offered as possible explanations for their findings.

The antibody findings in this study confirm those of earlier studies by Kaplan, Anthony, Chapman, Ayoub, and Wannamaker (29) and Dillon and Reeves (30) which indicate that the ASO response is poor after streptococcal skin infections, and that the anti-DNase B is of greater value in studying the immunological response to skin infection. In addition the antibody responses varied inversely with the mean initial titers, children with no rise having higher initial titers than those demonstrating a significant rise. High initial antibody titers may have resulted from respiratory streptococcal infections in the late winter or spring or from skin infections early in the summer. Studies of streptococcal respiratory disease have indicated that patients with low mean initial antibody titers will generally show a greater magnitude of rise (31, 32). These findings have resulted in several different interpretations (32). Further data and more extensive analysis of the antibody response in relation to initial titer are needed in patients with skin infections. In the present study the anti-Group A carbohydrate values tended to be high in these children on admission to the study reflecting the endemicity of streptococcal infections in this population and the tendency for antibodies to the Group A carbohydrate to remain elevated for prolonged periods of time (17).

The high percentage of streptococcal isolates (73%) which could be typed serologically with M-antisera in this study is partially explained by the predominance of one type (M-57) in three of the five families. This serotype is one of the newer described streptococcal pyoderma strains, and has been isolated from pyoderma-associated acute glomerulonephritis in Trinidad (2, 3).

The six Group A streptococcal serotypes recovered in this study were all recovered from normal skin sites and from skin lesions. There were similarities among the prevalent types in the high frequency of children who developed lesions if the same type was recovered from normal skin. However, 86% of children with M-type 57 developed lesions after the appearance of this type on normal skin and the interval between recovery from skin and development of lesions was shorter (7.3 days) than for the other types (range 11–14 days). There was no apparent difference in the risk of lesions developing if a particular streptococcal serotype appeared on the normal skin early in the study or in the middle of the study. The risk of new lesions developing at the end of the study could not be determined because new streptococcal serotypes rarely appeared then. There was a low risk of development of lesions after the recovery of streptococci of Group G or B from the normal skin, suggesting that these streptococci are of low pathogenicity for the skin.

The patterns assumed by different streptococcal serotypes as they move through families demonstrate that usually a new type enters and becomes predominant while a preceding type is at a peak or declining. Of interest is the family with four serotypes coexisting for periods of time, although one type (M-57) clearly accounted for the majority of positive cultures. This information cautions one against accepting readily, in patients presenting with nephritis, a single culture result as necessarily indicative of the etiologic nephritogenic strain. Skin lesions of different serotypes may be present simultaneously, so there is value in culturing fresh lesions and lesions in various stages of healing. The offending nephritogenic strain may have caused disease which preceded the development of lesions due to the currently isolated strain, but because of the relatively long latent period in pyoderma-related nephritis (6, 8, 33) the strain may no longer be present.

Thus, the present study amplifies previous knowledge of the epidemiology of streptococcal skin disease. Although the reservoirs of streptococci remain ill defined, the respiratory tract can be eliminated as a source of infection. Normal skin acquisition of the organisms appears to be a prerequisite to development of lesions. Local and environmental factors appear to be important determinants of the site of infection. The risk of developing impetigo is high after appearance of Group A streptococci on the normal skin.

Note added in proof. Since the submission of this manuscript a report of the appearance of streptococci in skin lesions before their appearance in the respiratory tract has been published (Bassett, D. C. J. 1972. Streptococcal pyoderma and acute nephritis in Trinidad. *Br. J. Dermatol.* **86** (Suppl. 8): 55). This report and the earlier ones from this laboratory (5, 10, 23) were based on observations at less frequent intervals.

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