

*The epidemiological cycles of chronic staphylococcal infections in households are discussed and the various methods of control that have been used are examined. The authors conclude there is no sovereign remedy and suggest a number of possibilities for research.*

## EPIDEMIOLOGY AND TREATMENT OF CHRONIC STAPHYLOCOCCAL INFECTIONS IN THE HOUSEHOLD

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"So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown." Book of Job 2:7.

STAPHYLOCOCCAL disease is one of the most common bacterial infections affecting the general population. According to unpublished figures from the U. S. National Health Survey, the estimated incidence per year of furuncles and carbuncles is about one million cases. This figure, which is probably an underestimate, according to Mrs. L. E. Bollo of the National Health Survey Division, was obtained through interviews of household members in a sample of the civilian noninstitutionalized population of the United States during the period of July 1, 1957, to June 30, 1959. An additional half million cases of styes were reported, and cases termed "abscess" or "cellulitis" of external sites amounted to about another half million.

More detailed information on incidence is found in the British literature in reports by general practitioners of the diseases commonly seen in their yearly practice. The incidence ranges from about 1.5 per cent of 2,000 pa-

tients followed by Horder (1954)<sup>1</sup> to approximately 4 per cent of 14,000 young adult males summarized by Logan (1954)<sup>2</sup> from reports of eight practitioners (five urban, three rural), and about 5 per cent of 1,550 patients observed by McGregor (1950).<sup>3</sup> Gould and Cruikshank (1957),<sup>4</sup> over a two-year study in a general practice in Edinburgh, noted a 5 per cent yearly incidence of staphylococcal infections. Of the 221 patients infected, 54 per cent gave a history of other lesions within the previous two years—these were classified as recurrent infections. In the other 46 per cent, the presenting lesion was regarded as an initial episode, although only 19 per cent gave no history of staphylococcal infections at some time in their lives.

More recently, Kay<sup>5</sup> reported on a study of 37 families in Manchester over a 12- to 24-month period in which he found about 9 per cent of individuals per year to have suffered from staphylococcal infections. The chance of recurrence of infection in such individuals was double the incidence of the general population, while the risk of recurrence



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in any member of the same family was  
four times the rate experienced by a  
family with no previous infection. Simi-  
lar detailed information has not been  
found in the American literature.

Chronic or recurrent staphylococcal  
lesions are most often superficial, affect-  
ing the skin and subcutaneous tissues.  
Table 1 presents the most frequent diag-  
noses made in a survey of staphylo-  
coccal infections in 44 general practices  
conducted in Australia in 1958 by John-  
son, et al.<sup>6</sup> Out of 2,118 staphylococcal  
lesions, 543, or one-fourth of the total,  
were described as chronic or recurrent.  
The major difference between both  
groups is the greater number of furun-  
cles in the chronic group. It is quite  
likely that the incidence of such minor  
lesions as pustules, which might not  
bring patients to their physicians, is  
actually higher.

The recurrence of infections seen in  
an individual has also been observed in  
certain families where lesions are pres-  
ent almost continuously in one or an-  
other member for prolonged intervals.  
Phyllis Rountree of Australia describes  
them as "staphylococcal families."<sup>7</sup> The  
natural history of such perpetually

occurring infections both within one  
person and within a family unit has  
remained obscure until relatively re-  
cently. Bacteriophage typing has helped  
to clarify staphylococcal epidemiology  
in these situations, just as it has in  
hospitals. The epidemiological cycle  
within the hospital and its role as a  
source of spread into the community  
have been reviewed elsewhere.<sup>8</sup> It  
should be noted, however, that although  
recurrent familial infections originate  
frequently from the hospital, there is  
no concrete evidence that hospital  
strains are more virulent than those of  
unknown origin. It is also worth point-  
ing out that the incidence of penicillin-  
resistant staphylococci from lesions in  
the community appears to be approach-  
ing that found in hospitals.<sup>5,6</sup>

The epidemiology of staphylococcal  
infections within the household presents  
several complexities. As an illustration,  
Table 2 presents one family closely ob-  
served by Hurst and Grossman<sup>9</sup> over a  
two-year period. Cultures were phage-  
typed at intervals, as indicated by the  
asterisk in the table and all contained  
the same strain—Type 80/81. It was  
introduced into the home by a four-day-

Table 1—Diagnoses of Staphylococcal Lesions Observed in General Prac-  
tice in Australia

(Adapted from Johnson, et al., 1960)<sup>6</sup>

	Total Group of Lesions		Chronic and Recurrent Lesions (1/4 of Total)	
	Number of Cases	Per cent of Total Cases	Number of Cases	Per cent of Total Cases
Furuncle	682	32.2	270	49.7
Abscess	253	11.9	41	7.5
Paronychia	163	7.7	27	5.0
Impetigo	159	7.5	37	6.8
Carbuncle	134	6.3	34	6.3
Pustule	109	5.3	30	5.5
Stye	58	2.7	26	4.8
Miscellaneous	560	26.4	78	14.4
Total	2,118	100.0	543	100.0



Table 2—Recurrent Familial Infections Due to Staph. aureus Type 80/81

(Adapted from Hurst, V., and Grossman, M., 1958)<sup>9</sup>

Age of Infant	Infant	Mother	Father	Siblings, Aged			
				2 years	4 years	6 years	8 years
4 days	Carrier*						
Intermittent boils, various family members							
3 months	Boil*						
4 months	Carrier*	Carrier*		Carrier*	Carrier*		
		Boils Impetigo					
7 months	Carrier*	Carrier*			Carrier* Furuncle*	Carrier*	Carrier* Furuncle*
7.5 months	Carrier*	Carrier*		Carrier*	Carrier*	Carrier*	
12 months					Furuncle		Furuncle
13 months		Carrier* Boil*				Carrier*	Carrier*
16 months							Carrier*
16.5 months					Anal Abscess		
17 months	Boils			Boils	Boils		
17.5 months					Carrier* Furuncle*		Carrier*
24 months					Furuncle*		

\* Indicates cultures phage-typed and demonstrated to contain 80/81.

old infant who had been born in a hospital where a nursery outbreak of impetigo was occurring. Nasal and throat cultures obtained from the infant at the time of hospital discharge proved him a carrier of the 80/81 strain, but he remained asymptomatic until the age of three months. During this interval various family members experienced boils which are presumed to have been caused by the hospital type although the bacteriological investigations had not yet begun. The characteristic epidemiological features demonstrated by this family are:

1. With the curious exception of the father, all members eventually developed lesions and

all were nasal or throat carriers on one or more occasions. The carrier state was intermittent since none yielded the 80/81 strain consistently.

2. Since the carrier state always preceded or accompanied sepsis, a certain amount of autoinfection seems probable although cross-infection also undoubtedly occurred.

3. An active lesion in one individual did not necessarily result in the immediate development of sepsis in others of the family. For example, after the mother's boil in the thirteenth month the family experienced no further disease until three and one-half months later.

4. The intervals at which any particular individual developed recurrent lesions varied from five months, in the case of the four- and eight-year-old siblings, to 14 months in the case of the infant.

5. The infectious strain continued to plague



this family for a two-year period, after which it disappeared spontaneously.

From such observations, it is apparent that staphylococcal disease within the household is characterized by a remarkable tenacity of the pathogenic strain despite occasional long remissions. Although these features have been noted by a number of investigators (Colbeck, 1949<sup>10</sup>; Wentworth, et al., 1958<sup>11</sup>; and Ian Smith, 1961<sup>12</sup>) they have been most thoroughly documented by Roodyn (1960)<sup>13</sup> who followed the disease course of 17 families over a seven-year period. In 6 of the 17 families, although there were multiple cases, the lesions were caused by different phage types of staphylococci, so that autoinfection was excluded. However, the

histories cited by Roodyn in the other 11 families are so illustrative of the characteristic infection cycle that one is redescribed here (Table 3). In this household a Type 52A/79 staphylococcus of unknown origin caused recurrent infections over a six-year period. All family members were afflicted on at least one occasion, and frequently they proved to be nasal carriers simultaneously. Twice—in 1954, and again in 1956—the infectious strain remained dormant for nearly a year. Had phage typing not been performed the prolonged persistence of this strain might seem almost unbelievable. Within the 11 households which Roodyn studied, the intervals at which lesions developed varied from 3 to 11 months. These long remissions, which are so characteristic

Table 3—Recurrent Familial Infection from Which *Staph. aureus* Type 52A/79 Was Repeatedly Isolated

(Adapted from Roodyn, L., 1960)<sup>13</sup>

Date	Mother	Father	Daughter Age 17	Daughter Age 13	Son Age 12
May, 1952	Boil of chin Nasal swab				
August, 1952	Boil of leg Nasal swab				
April, 1953				Boil of leg Nasal swab	
July, 1953		Abscess of axilla Nasal swab			
November, 1955					Boil of arm Nasal swab
July, 1957		Boil of axilla Nasal swab	Abscess of eyelid		
April, 1958					Boil of nostril
July, 1958		Boil of armpit			Abscess of eyelid
September, 1958	Wound of finger Nasal swab				



Table 4—Strains of *Staph. aureus* Known to Have Caused Recurrent Familial Infection

Group	Phage Pattern	Persistence Within Family	Source	Reference
I.	29/31	At least 3 months	Unknown	Harrison, 1948 <sup>15</sup>
	52A/79	1 month to over 6 years	Unknown	Roodyn, 1960 <sup>13</sup> Tulloch, 1960 <sup>16</sup>
	52/79/80	Less than 1 month	Unknown	Roodyn, 1960 <sup>13</sup>
	79	4 months	Hospital	Roodyn, 1960 <sup>13</sup>
	"80/81 complex"	1 month to 4 years	Hospital	Many reports, cited in Nahmias and Eickhoff, 1961 <sup>18</sup>
II.	3C	2 months	Unknown	Roodyn, 1960 <sup>13</sup>
	3B/3C	6½ years	"	"
	3C/55	7 months	"	"
	3C	A few days to months	"	Barrow, 1955 <sup>17</sup> Johnson, et al., 1960 <sup>6</sup> Tulloch, et al., 1960 <sup>16</sup>
	55	"	"	
	71	"	"	
	55/71	"	"	
	3B/55	"	"	
	3B/55/71	"	"	
III.	42E	At least 2 months	Unknown	Tulloch, et al., 1960 <sup>16</sup>
	57 ("W")	10 months	Hospital	Colbeck, 1949 <sup>10</sup>
	Miscellaneous Untypable	Over 5 years	Unknown	Roodyn, 1960 <sup>13</sup>

of chronic staphylococcal disease, make evaluation of treatment extremely difficult, as will be pointed out later.

Strains within the "80/81 complex" comprising strains typing with phages 52, 52A, 80, 81 either alone or in various combinations (Nahmias, et al., 1961)<sup>14</sup> are frequently recovered in recurrent and chronic staphylococcal infections, comprising 56 per cent of 419 such cases in an Australian survey (Johnson, et al., 1960).<sup>6</sup> However, it should be emphasized that many other phage types in Groups I, II, and III, as well as untypable strains, have been re-

covered from "staphylococcal families," as demonstrated in Table 4.

From these and other observations, Figure 1 has been prepared to present the two cycles which are believed to be involved in the epidemiology of household infections: that of cross-infection from human to human directly or indirectly, in which animals could be associated on occasion, and that of auto-infection, from one site of an individual to another site on his own body. Control measures which have been or could be applied at one point or other of these cycles will be focused more sharply in



# STAPHYLOCOCCAL INFECTIONS

this way as they are discussed in some detail.

The source of the staphylococcus in the household can be an individual who is either a carrier or has a lesion. The work of Hare and Cooke<sup>18</sup> suggests that individuals with discharging lesions which cannot be contained by a dressing are the most likely to contaminate themselves and their environment. How-

ever, the exact role of the environment (reviewed elsewhere<sup>8</sup>) as a source or reservoir of staphylococcal infections awaits more definitive studies.

The evidence supporting the possibility of animals acting as a source or reservoir of infection has been reviewed by Courter, et al.<sup>19</sup>

The evidence supporting the importance of either cross-infection or autoin-

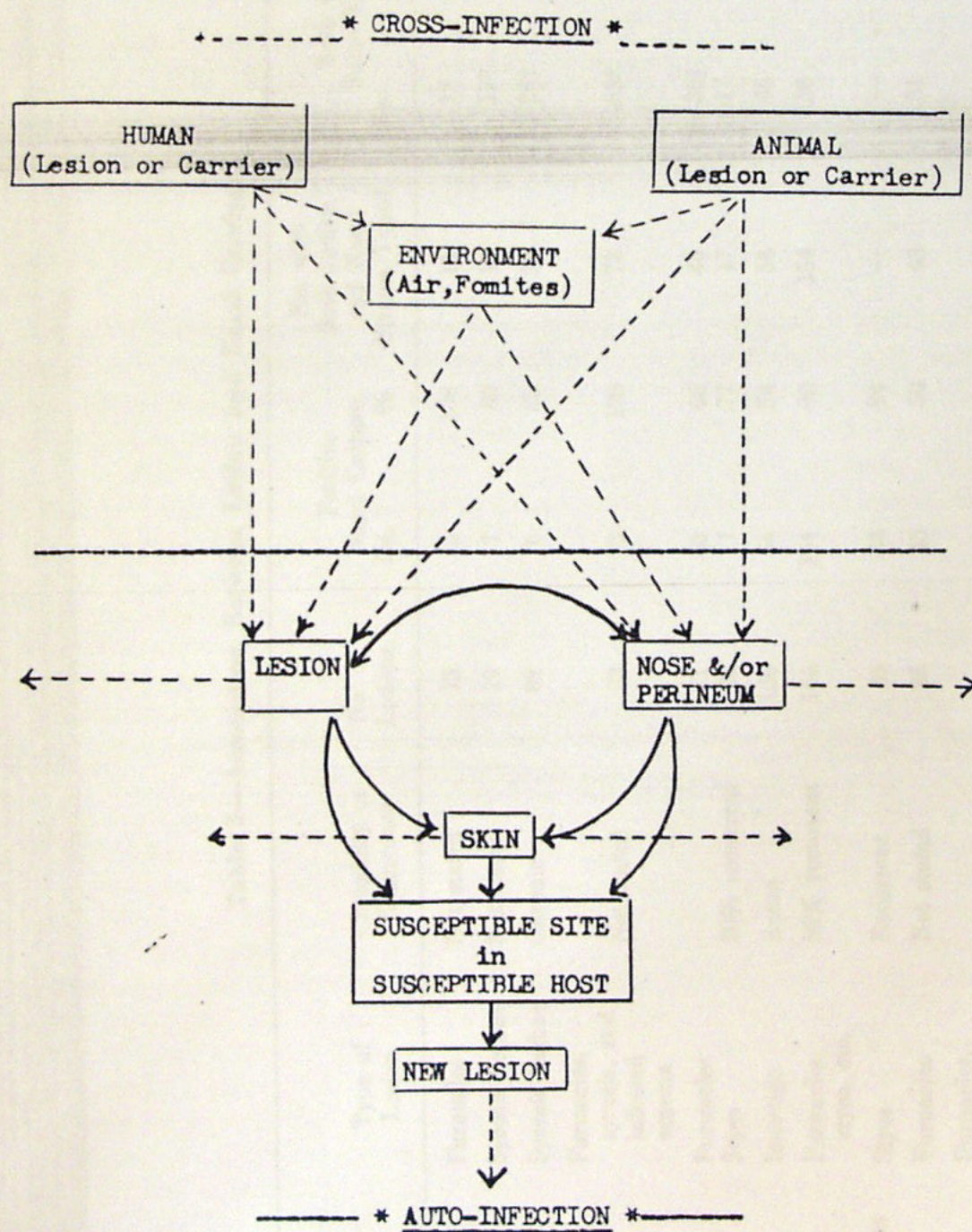


Figure 1—Epidemiological Cycles of Staphylococci in the Household



Table 5—Association Between Lesion and Nasal Carriage

Author	Type of Lesion	Chronicity or Recurrence	No. of Lesions	Positive Nasal Culture No.	%	No. with Both Lesion and Nasal Strains Typed	Both of Same Type No.	%	Per cent of All Lesions with Same Type as Nose
Fisk, '44 <sup>20</sup>	Furuncles	Not stated	15	15	100	15	12	80	80
Hobbs, '47 <sup>21</sup>	Sycosis barbae	Not stated	19	17	80	17	17*	100	80
Valentine, '52 <sup>22</sup>	Sycosis barbae	Chronic	89	76	85	25	12-24†	76-96	—
Tulloch, '54 <sup>23</sup>	Furuncles, sycosis, and infected eczema	Not stated	73	73	100	73	45-63†	63-83	63-83
Roodyn, '54 <sup>24</sup>	Furuncles	20% recurrent	71	48	68	48	26-36†	54-79	37-51
Barrow, '55 <sup>17</sup>	Styes		22	17	77	17	17	100	77
Gould, '57 <sup>4</sup>	Impetigo	Acute	100	54	54	54	46	85	46
	Furuncles, styes, etc.	54% recurrent	166	154	93	154	128	83	77
Copeman, '58 <sup>25</sup>	Styes	Recurrent	36	34	94	—	—	—	—
Ruys, '58 <sup>26</sup>	Furuncles	Not stated	85	43	50	43	31	72	36
Johnson, '60 <sup>6</sup>	Furuncles, abscesses, styes, etc.	Chronic	419	174	42	174	121	70	29
Roodyn, '60 <sup>13</sup>	Infections, skin, eye, etc.	Recurrent	23	18	80	18	16	89	70
Tulloch, '60 <sup>16</sup>	Furuncles	Recurrent ✓	58	58	100	58	51	88	88
Kay, '62 <sup>5</sup>	Infections, skin, eye, etc.	Not stated	92	—	—	—	63	68	68

\* Serological typing. All others by phage typing.

† Including occasions where both lesion and nasal strains were nontypable.

— Data inadequate.

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fection in the causation of recurrent lesions in the same individual and other members of his family will be brought out in the following discussion which will review:

1. The association between lesion and nasal and/or perineal carriage, and
2. The association between nasal and/or perineal carriage and skin colonization.

The importance of the susceptibility of a particular site to infection as well as general mechanisms in host susceptibility will then be discussed.

# I. Association Between Lesion and Nasal and/or Perineal Carriage

## (a) Nasal Carriage

Table 5 presents the experience of several workers in recovering the same staphylococcal strain from both lesion and nasal specimens. Since Fisk (1944)<sup>20</sup> applied bacteriophage typing, this method has been very useful to establish the similarity between staphylococcal strains from various sites. The first column reveals that the per cent of positive nasal cultures associated with lesions ranges from a low of 42 per cent in Johnson's studies<sup>6</sup> to 100 per cent in Fisk and Tulloch's series.<sup>20,23</sup> Where both nasal and lesion strains were typed, the finding of both being the same type ranges from 54 per cent to 100 per cent. The final column, however, discloses that for all lesions where nasal cultures were obtained, including those with negative nasal carriage, the per cent ranges from a low of 29 per cent to 88 per cent. There are several possible reasons to explain this wide discrepancy in results by different workers:

(1) The Chronicity of the Staphylococcal Lesion—Although Johnson, et al.,<sup>6</sup> found only a 29 per cent carrier rate in their 419 chronic cases, they found the carrier rate in 1,195 primary cases to be 21.6 per cent. However, even this small difference noted between the

two groups (7.4 per cent) was found to be statistically significant at the 1 per cent probability level. Other reports of low association are those of Barrow (1955)<sup>17</sup> who was studying impetigo, which is not commonly recurrent, and of Ruys, et al. (1958)<sup>26</sup> who did not differentiate acute from chronic furunculosis in their study of miners in the Netherlands. In series where recurrence was high (Gould and Cruikshank (1957),<sup>4</sup> Roodyn (1960),<sup>13</sup> and Tulloch, et al. (1960)<sup>16</sup>) the association was higher than 70 per cent.

(2) The Site of the Lesion—It would appear logical to assume that lesions around the face, such as styes, being closer anatomically to the nose, would be more intimately associated with nasal carriage. This is suggested from the data of Kay<sup>5</sup> and by the report of Roodyn<sup>24</sup> where the per cent association of nasal carriage with boils was only about 50 per cent, while association with styes was about 80 per cent (Table 5).

(3) The Time at Which the Nasal Cultures Are Taken—Although most of the patients with recurrent lesions appear to be persistent nasal carriers, for as long even as seven years,<sup>13</sup> some of these individuals might be intermittent carriers, with the consequence that a nasal culture taken at the wrong time might be negative. In addition, nasal cultures may have been obtained while patients were on antibiotic therapy which can temporarily suppress staphylococci.

This association between lesions and carrier state is of great importance as it might help differentiate the cycle of cross-infection from that of autoinfection (Figure 1).

## (b) Perineal Carriage

Hare and Ridley (1958)<sup>27</sup> and later Ridley (1959)<sup>28</sup> pointed out the possible importance of perineal carriers in staphylococcus epidemiology. They

\* Serological typing. All others by phage typing.  
† Including occasions where both lesion and nasal strains were nontypable.  
— Data inadequate.



demonstrated that there were individuals who were perineal carriers but not nasal carriers, and that the staphylococci were not in the perineum as contaminants from the neighboring anal orifice, but actually were capable of multiplying in that site. In addition, they found that strains from individuals who were both nasal and perineal carriers were identical. Ian Smith<sup>12</sup> found in a study of 57 families in Iowa that individuals with lesions occurring mainly below the waist tended to be perineal carriers. Kay<sup>5</sup> has also intimated this correlation from his experience. Such observations may explain the lack of success obtained when only the nasal site is treated locally.

## 2. Association Between Nasal and/or Perineal Carriage and Skin Colonization

Gillespie, et al. (1939),<sup>29</sup> and later Miles, et al. (1944)<sup>30</sup> observed that about 25 per cent of 69 and 227 individuals, respectively, had coagulase-positive staphylococci recovered from both nose and skin over the wrist. Williams (1946)<sup>31</sup> went on to study in greater detail this association in 65 subjects. He found in 31 cases the same phage type from both nose and skin, and in 18 cases untypable strains from both sites. Williams attributed the 16 cases where nasal and skin strains were of different types to the fact that more than one phage type of staphylococcus may be present on the skin. More recently, Roodyn (1960)<sup>13</sup> has also demonstrated, using a special technic for recovery of staphylococci from deeper layers of the skin, that organisms could persist there for longer periods than on the superficial skin. This substantiates earlier observations of Pillsbury and Kligman in the United States (1954)<sup>32</sup> as well as those of Röckl and Müller in Germany (1959),<sup>33</sup> the latter group finding that about 25 per cent of bacteria are

located beneath the superficial layers of the skin. These observations may help explain the difficulties inherent in complete skin sterilization, and offer some basis for the latent periods of freedom from lesions found in some individuals with recurrences months or years apart.

The importance of the skin in the epidemiological cycles presented in Figure 1 has been well established by the studies of Duguid and Wallace (1948)<sup>34</sup> and later by Hare and Ridley (1958).<sup>27</sup> Dissemination from skin to clothing, bedding and the air, and thence to other sites of the individual or to others can thus occur. White (1961)<sup>35</sup> more recently made sweep plates of patients' clothing by sweeping Petri dishes over the anterior surface of their gowns from shoulder to groin three times on each side. He recovered the same staphylococcal type from both sweep plate and the patient's nose in 38 out of 44 cases. He concluded that in the remaining six patients and in 20 other patients who were noncarriers, but had positive sweep plates, the staphylococci were presumably obtained from sources other than the patient's nose. White also showed<sup>36</sup> that staphylococci could be recovered from 5 per cent of skin cultures in patients who were carriers of less than 100,000 colonies from a nasal swab. On the other hand, staphylococci could be isolated from 44 per cent of skin cultures in patients who were nasal carriers of more than 100,000 colonies per swab.

Fecal carriage of staphylococci should also be mentioned. Since it has only been studied in hospital populations, particularly in relation to concomitant antibiotic therapy,<sup>37-39</sup> its relative importance in the household epidemiological cycles remains to be evaluated.

## The Susceptible Site

Physicians are familiar with staphylococcal lesions which develop in pa-

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tients with various dermatoses, such as eczema or seborrhea. For instance, Cruikshank (1953)<sup>40</sup> cites the study of Twiston Davies, et al., in 1945 where 148 out of 200 cases of impetigo were found to be secondary to seborrheic dermatitis. An abraded or traumatized skin can readily be visualized as a susceptible site for infection or re-infection. As an example where the local condition of the skin may be responsible, Cruikshank (1953)<sup>40</sup> also cites J. R. May's studies which showed that although bullous impetigo is rare in adults, as many as 9 per cent of British troops in Singapore and Hong Kong developed these staphylococcal lesions, most commonly in the axillae. This was attributed to the moist, sodden condition of the skin in the axillae resulting from continual sweating and lack of ventilation in a hot, humid climate. Another example is that offered by the observations of Hellier (1955)<sup>41</sup> on the factors of importance in the etiology of chronic paronychia. These lesions were found most frequently in patients with vascular abnormalities and in those whose work involved exposure to water. Local metabolic factors inherent in the skin, such as glucose metabolism in diabetics, may also be of importance in site susceptibility.

#### The Susceptible Host

Systemic factors that are responsible for the occurrence in certain individuals of recurrent staphylococcal infections, while others remain free of lesions, are poorly understood. Why, for instance, the father (Table 2) remained free of infections, even though in close contact with six other afflicted members of his family, remains a scientific mystery. Hormones may be of importance—diabetes has been mentioned. Other hormonal effects may contribute to the occurrence of pustular disease around puberty. It would be of interest for

someone to study the occurrence of recurrent staphylococcal lesions in a group receiving steroid therapy versus a similar group not receiving these hormones. Morginson and associates (1959)<sup>42</sup> have found that many of their cases with chronic staphylococcal dermatoses were low in gamma globulin. However, these authors do not give any actual figure for what they considered a low gamma globulin level. In addition, their definition of chronic staphylococcal dermatosis, in which they group conditions such as seborrheic dermatitis, intertrigo and eczematoid dermatitis, is open to some question.

The importance of white blood cells in relation to susceptibility to recurrent staphylococcal infection is brought out in an "experiment in nature" other than agammaglobulinemia. Kostmann (1956)<sup>43</sup> reported from Sweden on a familial type of agranulocytosis. The first signs of the disease in the affected children were due to infections consisting primarily of skin lesions and recurring until their early demise. Recurrent cutaneous infections have also been noted in cyclic neutropenia,<sup>44</sup> a condition where neutrophils are only temporarily depressed.

A review of the sparse knowledge on the subject of host susceptibility has been presented elsewhere<sup>8</sup> and attempts at increasing host resistance with immunogenic agents will be discussed shortly.

#### Methods of Control

By reviewing Figure 1 one can see the rationale behind the use of a particular approach to control.

##### 1. Control of Lesions and the Nasal Carrier State

For control of the lesion and/or nasal carriage state, two approaches at treatment have been used—systemic and



local. The evidence that either method of therapy can influence the course of the nasal carrier state or of skin infections has been quite difficult to evaluate. This is due to the problem of defining relapses and recurrences on the one hand, and reinfection with the same or different organisms on the other. Obviously the problem depends upon the environment in which the treatment is carried out. Moreover, the treatment in the family of some of its members, and in the hospital of other patients in the ward, will have a secondary effect on the remaining population which may alter the total ecological picture.

Another important factor is the spontaneous recovery, relapse, and superinfection rate of a cohort of nasal carriers which may vary greatly from one time to another and in one clinic to another. Even in the same hospital, in studies done by the same laboratory, the spontaneous change rate was found by one of us (M.L.) to vary at different times.\*

It is not surprising then that there are differences between spontaneous loss of carrier state in different laboratories. More consistent, however, is that whenever serial phage typing was applied, there was evidence of some degree of superinfection. The rate of superinfection has been greater among hospitalized patients, accounting for over half of the persistently positive cultures in some groups.

In spite of this variation, treatment with a wide variety of antistaphylococcal antibiotics has been found to speed the removal of nasal staphylococci.\* This is particularly true if superinfections are not included in the total outcome. Failure to continue therapy was associated with a return of positive cultures for the original phage type almost to the level expected for the same period of time without therapy. There is also some indication that multiple drug therapy was more active than individual drugs. These results suggest

that while systemic antibacterial treatment can influence the nasal carrier state, prolonged use and heavy dosage seem necessary. In certain individuals where the carrier state interferes with employment, such prolonged therapy may allow them to work with reasonable safety.

The same principle appears to be involved in the treatment of furunculosis. Uniform success was initially claimed with almost every new antistaphylococcal agent which appeared on the scene. However, the real evaluation must be made not in terms of the patient with acute furunculosis but in the one with the recurrent problem. Thus when a patient is treated at the time of the first episode of furunculosis, the spontaneous relapse rate may be only from 20 to 30 per cent. However, if several episodes have already occurred, most patients will probably have more attacks in the future. It is in this group of patients that drugs are best evaluated. Various regimens were tried by one of us (M.L.) in 44 such patients of combinations of two of the following drugs: chloramphenicol, erythromycin, novobiocin and oleandomycin, for periods of from three weeks to six months. It was found\* that unless therapy is continued for a considerable period and unless large doses are used, the relapse rate is high. In most situations, systemic antibiotics are reserved for serious infections. They can be used for a shorter period of time to give symptomatic relief, and if used early enough, to avoid abscess formation in local lesions. If antibiotics are to be used to eradicate the carrier state or recurrent lesions, a relatively expensive and sometimes toxic course of therapy is needed. Such treatment should not be undertaken unless other forms of therapy have failed and unless there is a complete understanding on the part of the

\* Tables with supporting data are available upon request.

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patient. It is quite possible that the new orally active penicillinase-resistant penicillins will greatly increase the opportunity to use such a prolonged form of oral therapy in selected cases.

#### Local Therapy

##### (a) The Lesion

Local therapy in the case of lesions is mostly useful in the surgical incision and drainage that may be required. Although various topical antibacterial agents have been tried, their greatest use probably resides in the prevention of dissemination of organisms from the lesion site to other areas of the body. In addition, an adequate dressing should, according to the data of Hare and Cooke,<sup>18</sup> curtail much of the contamination and potential spread to the individual himself as well as to other individuals and the environment.

##### (b) The Nasal Carriage State

The first attempt at the application of some antibacterial agent to the nose was apparently made by Delafield, et al., in 1941.<sup>45</sup> They used various antiseptics, including penicillin, in the form of snuff. Ever since that Elizabethan method of administration, other techniques have been used, including sprays, ointments, creams, and even sesame oil suspensions. A multitude of antibacterial agents have been used either singly or in combination. These include: sulfathiazole, penicillin, streptomycin, the tetracyclines, chloramphenicol, tyrothricin, gramicidin, framycetin, chlorhexidine, neomycin, Kanamycin, bacitracin, and methicillin (staphcillin).<sup>45-52</sup>

Burrows, et al., in 1945,<sup>46</sup> Hobbs, et al., in 1947,<sup>21</sup> and Valentine and Smith in 1952,<sup>22</sup> using penicillin, both in the nares and over the infected skin, were able to reduce relapses of sycosis barbae or furunculosis. Copeman (1958)<sup>25</sup> reported great success in the therapy of recurrent styes by the nasal application of a neomycin-gramicidin ointment.

Gould and Cruikshank (1957)<sup>4</sup> found that in 127 patients with recurrent furunculosis, 96 developed no further lesions and 12 showed a decrease in the number of their lesions when nasal antibacterial ointments were applied.

##### (c) The Perineal Carriage State

Tulloch, et al. (1960)<sup>16</sup> have used hexachlorophene baths or powder for controlling the perineal carrier state. Ian Smith (1961)<sup>12</sup> advocates the use of bacitracin to the perineal area.

##### (d) The Skin

Approaches at this point have consisted of good principles of hygiene with frequent baths and hand washing with such agents as hexachlorophene, even the use of sterile underwear and handkerchiefs.

In one of the rare control studies in the treatment of chronic furunculosis, Tulloch, et al. (1960)<sup>16</sup> bring out the need for control at all points in the epidemiological cycle (Figure 1). Thus, they used:

For the lesion: Swabbing the boil-bearing area twice a day with a mercuric chloride solution.

For the nares: Neomycin with gramicidin or bacitracin cream two to three times daily for at least three months.

For other carrier sites: (If eye swabs positive) without lesions—the same cream.

(If eye swabs positive) with lesions—the same cream plus hydrocortisone.

For otitis externa—neocortef drops.

For perineal carriers and skin: Hexachlorophene baths—every day for one week; then every other day for two more weeks; then twice weekly for six to eight weeks.

Or: "Zac" talcum powder (with 0.3 per cent hexachlorophene) daily to the perineum, buttocks, and trunk.

In addition to this multiple approach at control, in five cases who failed to respond, eradication of family sources of reinfection resulted in cures (Table 6). This brings up the need of control of cross-infection from other family members (Figure 1), where the meas-



**Table 6—Treatment of Chronic Furunculosis**

(Adapted from Tulloch, et al., 1960)<sup>16</sup>

	Total Patients	Patients Cured	Per cent Cure Rate
Controls	23	3	13
Treated	33	27 (5 also needed Rx of family members)	82

ures mentioned above would need to be used concomitantly. In addition, precautions against vectors, such as bedding, baths, and so forth, which appear to be of some value in hospitals (e.g., Gillespie, et al., 1961<sup>53</sup>) might prove helpful, although data on household environmental aspects are not available.

## 2. The Susceptible Site

Prompt and proper management of various underlying skin dermatoses, skin trauma, or diabetes should hopefully reduce infection or reinfection with staphylococci.

## 3. The Susceptible Host

Interest in immunogenic agents, which was stimulated in great part by the Bundaberg disaster in 1928, and faded with the advent of antibiotics, at least in America, has been resurrected in recent years by some of the dismaying experiences in our hospitals and community. The European experience with toxoids and vaccines is reviewed in the monographs of D'Antona (1958),<sup>54</sup> Elek (1959)<sup>55</sup> and Worms (1960).<sup>56</sup> Whereas these agents appear to be widely used in certain European countries, physicians in America and Great Britain have been more reluctant to

employ them. This is probably because of the lack of appropriate control studies, in a condition with prolonged remissions and spontaneous cure, where long follow-up studies are indicated. In addition, some of the agents used cause certain local or systemic reactions.

It was deemed of interest for purposes of this presentation to obtain information on the staphylococcal immunogenic agents manufactured in the United States. Seven companies\* were kind enough to send us information on their products. Two companies produce a vaccine prepared of a mixture of *Staph. aureus* and *Staph. albus*. Another company produces a vaccine of a mixture of *Staph. aureus*, *Staph. albus*, streptococci, pneumococci, and *E. coli* prepared by treating the bacterial cells with specific immune rabbit serum. Another product consists of antigens of staphylococci lysed by bacteriophages to which toxoid is added. Two other products comprise both vaccine and toxoid, and one toxoid only. A wide variety of strains of *Staph. aureus* is used in the various vaccines produced. In the preparation of toxoids the manufacturers follow Tentative Staphylococcus Toxoid Requirements dated August 25, 1938, of the Division of Biologics Standards of the National Institutes of Health.

The three types of immunogenic agents that are available then are vaccines, toxoids, or combinations of the two.

### Vaccines

Besides the commercial vaccines, physicians, e.g., McCoy (1960),<sup>57</sup> have used autogenous vaccines, i.e., preparations of the staphylococci recovered from the patient's lesion and killed by various methods. David Smith of Duke University<sup>58</sup> has used such vaccines for over

\*Eli Lilly, Lederle, Merck Sharp and Dohme, National Drug, Parke Davis, Sherman, and Squibb.

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30 years in the treatment of chronic or recurrent staphylococcal lesions. He believes the mechanism of action of such vaccines in hyposensitization rather than immunization. Greenberg and his associates in Canada,<sup>59,60</sup> on the other hand, believe that immunity to staphylococcal infections resides in the development of antibodies with a marked antibacterial activity. They have developed a polyvalent somatic antigen by combining enzyme (dornase)-lysed fractions of a number of phenolized heat-killed vaccines prepared from different phage types of *Staph. aureus*. They found in experimental animals (hamsters and rabbits) that this polyvalent vaccine protected them against challenge with both lethal and skin-infecting doses of 36 test cultures. They are presently attempting to utilize similar vaccines in human beings.

#### Toxoids

Of the many antigens, both structural and extracellular produced by staphylococci, the  $\alpha$ -hemolysin has received greatest prominence. The only present legal requirement of efficacy for commercial toxoids is that they should conform to certain standards of ability to stimulate the production of anti  $\alpha$ -hemolysin.\*

Interest is being revived in the non-hemolytic leukocidin of Pantan and Valentine (1932).<sup>61</sup> The activity of leukocidin has been found by Woodin (1961)<sup>62</sup> to be due to two synergistic proteins F and S which are antigenically distinct with each being inactive alone. Gladstone, et al. (1962)<sup>63</sup> and Mudd, et al. (1962)<sup>64</sup> have set out to study leukocidin in greater detail as a possible important constituent for providing immunity to staphylococcal infections. Their studies comprised:

\* Memorandum to Manufacturers of Biological Products, dated January 10, 1936, relating to the U. S. Standard *Staphylococcus* antitoxin.

- A method of assay of anti-F and anti-S leukocidal components in serum.
- A procedure for standardization of test toxins.
- Suggestions for a Standard of Reference for antileukocidins.
- A normal value for human beings of anti-leukocidin with a mean of 2 units/ml.
- A higher titer of antileukocidin in response to several staphylococcal lesions of six to seven times normal value, whereas the anti  $\alpha$ -hemolysin titer was less affected.
- Administration to human populations under controlled conditions of various products (Institut Pasteur "Divasta," Sclavo Toxoid (Siena), Connaught Laboratories toxoid, Lederle toxoid, polyvalent somatic antigen vaccine (Greenberg) and Staphage (Delmont Laboratories). Whereas anti  $\alpha$ -hemolysin was regularly elicited by all toxoids, none of the four products elicited significant responses in terms of antibodies to F and S leukocidins.

From these observations, it was suggested that controlled investigations be carried out by complementing existing immunogenic agents with leukocidin toxoid.

#### Vaccines and Toxoids

Besides commercial combinations of vaccines and toxoids, Dr. H. O. Dillenberg of Canada<sup>65</sup> has been using since 1957 polyvalent staphylococcal vaccine, containing the prevalent phage types of *Staph. aureus* in Saskatchewan and a reinforcing dose of  $\alpha$ -toxoid. Using a questionnaire method to obtain medical testimonials as to the efficacy of this regimen (46 per cent of questionnaires returned), a curative effect of 83 per cent of 536 cases of chronic staphylo-dermatosis was found. The author concluded by suggesting that this product might merit trials elsewhere.

#### Gamma Globulin

Morginson, et al. (1959)<sup>42</sup> administered gamma globulin to 59 patients with chronic staphylococcal dermatosis and claimed good to excellent results in 83 per cent of patients. The ever-present question of adequacy of length of follow-up comes up with this study as



it has so often in the past and as it should in any future studies of this problem.

We have presented the epidemiological cycles of chronic staphylococcal infections in individuals and in families and have discussed the varied control approaches that have been used. We would like to end by quoting from Delafield<sup>45</sup>—of antiseptic snuff fame—who, 20 years ago “snuffed out” the hope of those who saw an easy solution to the problem of infection:

“There is one conclusion to which, we think, all workers in this field will subscribe. There is no sovereign remedy. If the problem is solved, it will be by strengthening all possible defenses, not by developing some and neglecting others, though we may be able to allot priorities when we know more than we do now. . . .”

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