people, that only 35 per cent were considered to be leading nearly normal lives at the end of ten years.

It is interesting that of the 34 patients who died in Groups A and B, 70 per cent of their patient years of aortic insufficiency were spent in Class I (asymptomatic). Once symptoms of disability ensued, the average life span was four and five-tenths years. The duration in Class IV, however, was always less than one year and often even briefer.

Nine patients died with active rheumatic carditis, and 5 with subacute bacterial endocarditis. Since rheumatic carditis now responds favorably to steroids, and subacute bacterial endocarditis to antimicrobial therapy, such deaths may often be averted.[4] In 13 cases death was attributable to progressive cardiac failure some time between the end of the third and the middle of the fourth decade. The increased effectiveness of modern diuretic regimens would now reduce mortality in this group. Sudden death, a familiar complication of aortic-valve disease, occurred in 7 patients previously asymptomatic.

A comparison between the living and deceased groups before the onset of symptoms demonstrates no difference between them.

Summary and Conclusions

The long-term clinical courses of 81 patients with basal diastolic murmurs and mitral stenosis, 35 of whom died, are presented. Thirty-one patients had adynamic aortic insufficiency. In 9 patients th basal murmur had regressed.

All patients had moderate or marked cardiac en largement. The average duration of the asymptomati state was fifteen and one-tenth years, representing 8(per cent of the total patient years of observation.

Once symptoms developed, the average duratio of partial or complete disability was only two year: before death.

Death was related to progressive cardiac failure in 13, carditis in 9 and subacute bacterial endocarditis in 5, and was sudden and unexpected in 7 cases. Many of these deaths could now be prevented with current antibiotic, steroid and diuretic regimens.

This study demonstrates that the combination of basal diastolic murmurs, with or without the peripheral signs of aortic insufficiency, and mitral stenosis is compatible with many years of asymptomatic living. This fact should be kept in mind when surgical intervention is considered.

We are indebted to Dr. May Wilson for guidance and suggestions.

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MEDICAL PROGRESS

STAPHYLOCOCCAL INFECTIONS IN HOSPITALS (Continued)*

Recent Developments in Epidemiologic and Laboratory Investigation

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The Susceptible Host

It has been observed from earliest reports on staphylococcal disease that in certain groups staphylococcal infections are particularly likely not only to develop but also to have a fatal outcome.[4,136]

With the use of clinical or epidemiologic observations several factors have been correlated grossly with susceptibility to staphylococcal infections: general factors, such as age, sex, race and nutritional or metabolic status; and predisposing diseases, such as diabetes, cystic fibrosis, agammaglobulinemia, agranulocytosis, neoplasms, chronic lung disease, influenza and other viral infections. Other related factors are trauma, operative wounds, foreign bodies, burns, eczema and other dermatitides, urinary catheterization, intravenous administration and steroid and antibiotic therapy.

Two of the detailed studies illustrating the importance of host factors are those of Farrer and Macleod[21] and Minchew and Cluff.[22] The two studies differ in the age, sex and race attack rates, probably reflecting the type of patients frequenting these two hospitals. However, both studies agree on the high infection rate among patients who suffered from chronic diseases of one kind or another. In particular,

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patients with neoplasms and burns proved to be an extremely high-risk group.

It is apparent that a better knowledge of certain host factors is necessary to uncover some of the finer points involved in the susceptibility or resistance of particular hosts. Cluff and his associates have set out to elucidate this problem in a series of studies.[90,137,138] They first reviewed some of the work on immunity and hypersensitivity in staphylococcal infections, pointing to the influence of nutritional factors and metabolic disturbances in increasing host susceptibility. Experimentally, they demonstrated in rabbits[137] that increased susceptibility to infection was associated with the development of delayed hypersensitivity unaccompanied by the appearance of demonstrable serum antibody. They then showed that early inflammation produced in different ways could increase the infectivity of staphylococci. Greater resistance to infection in necrotic tissues, however, could be obtained with alpha-hemolysin antibodies, either actively or passively acquired, whose function was presumably the prevention of leukocytic destruction. In addition, these workers[138] found that bacterial endotoxin increased the infectivity of staphylococci in rabbit skin, probably again via an antileukocytic effect. The implications of these experimental studies as they become applied to the human host should prove of much future interest.

There has also been an increase in work on serologic tests for staphylococcal infection. Various antibodies are being found with the use of different technics, and it is difficult to ascertain from these reports whether identical, similar or completely different antibodies are being measured. Many of these tests have been evaluated only in normal populations, so that their relation to active infection is still to be determined.

A list of the various investigations made since 1950 is presented in Table 2. Earlier work is available in Elek's monograph.[41] The antibodies are further differentiated as those transferred via the placenta and those apparently not so transferred. Antibody to the erythrocyte-coating polysaccharide is poorly transferable in the placenta, and its titer rises from four months onward.[141] In two of the antibodies studied[139,148,149] that pass the placenta — anti-alpha-hemolysins and the Rantz antibody — there is a decrease in titer in the first few months of life, followed by an increase as the infant grows older. The level of the coagulase-reacting factor[142] is low before two years and increases thereafter.

Although antibodies to various factors have been found in normal serum — for example, antihyaluronidase,[140] antihemolysin[139,143,144] and antileukocidin[107,144] — there appears to be a significant increase in titer in patients with acute or chronic staphylococcal infections. This increase is more pronounced with antileukocidin,[107] which appears to afford better protection than antihemolysins in newborn infants. Preliminary investigations with the mouse protective-antibody test[146] suggested that patients with chronic furunculosis had a lower titer than noninfected patients, but this awaits further study.

Another interesting antibody has recently been described.[145,150,151] This is an antibody to antigen A, an extract of Cowan Type 1 strain, which is probably a polysaccharide fraction. This antibody factor has been found in 100 per cent of 1500 normal human serums and in several samples of cord serum and human colostrum. On the ileum of guinea pigs the antigen has a toxic effect that can be neutralized by either normal human serum or serum from rabbits immunized with a Cowan Type 1 strain. Both serums possess antibodies to antigen A. The relation of this antibody to infection and to other antibodies, such as the Rantz antibody, awaits further study. The Rantz antibody,[148,149] which can be titrated with hemagglutinating technics using nonspecies-specific bacterial substance as an antigen, has yet to be related to clinical infection. Wiley[101] has tested serum from normal blood donors for anticapsular antibodies and found that 80 per cent had demonstrable titers.

TABLE 2. *Staphylococcal Antibodies as Determined in Various Studies.*

Source of Data	Year of Report	Type of Antibody or Serum Factor Tested	Placental Transfer
Vahlquist et al.[139]	1950	Anti-alpha-hemolysin	Yes
Bergquist[140]	1951	Antihyaluronidase	—*
Rountree & Barbour[141]	1952	Antibody to erythrocyte-coating polysaccharide of staphylococcus	No
Rammelkamp & Lebovitz[142]	1956	Coagulase reaction factor	—*
Lack[143]	1957	Anti-alpha-hemolysin	Yes
Towers & Gladstone[144]	1958	Anti-alpha-hemolysin & anti-PV leukocidin	—*
Sebek et al.[107]	1958	Anti-alpha-hemolysin & antileukocidin	—*
Jensen[145]	1958	Antibody to antigen A (extract of Cowan Type 1 — polysaccharide?)	Yes
Fisher[146]	1959	Mouse protective antibody	Yes
Neter et al.[148,149]	1959, 1960	Hemagglutinin to nonspecies-specific substance (Rantz antibody)	Yes
Quie & Wannemaker[147]	1960	Inhibitor of satellite proteolysis (Mueller phenomenon)	Yes
Wylie[101]	1960	Anticapsular antibody	—*

*Not reported.

More recently, Quie and Wannemaker[147] identified in human serum an inhibitor of staphylococcal satellite proteolysis (Mueller phenomenon). This phenomenon, peculiar to coagulase-positive staphylococci, is characterized by the appearance of a satellite zone of multiple, discrete areas of clearing at some distance from a staphylococcal colony growing on blood agar. The inhibitor in the serum is believed to be an antibody and can pass the placenta.

In summary, serologic technics have become available in recent years, including a method for obtaining high titers of antibody from the ascitic fluid of mice[152] and one for stimulating antibody production by

implantation of staphylococci in the peritoneal cavity of rabbits.[153] Use of serologic technics might provide helpful information in the following areas: the definition and progression of "infection" with the staphylococcus on the basis of host response (this is particularly important in an understanding of the asymptomatic state); and the definition of antibodies of importance in the host's resistance to staphylococcal infection, with the possibility of using such antibodies for prophylaxis or treatment.

The subject of chemoprophylaxis of particularly susceptible persons has been thoroughly reviewed by Finland in a series of three monographs[154-156] pointing out the few situations in which chemoprophylactic agents are of established value, as well as the great number of cases in which they are of no value or else are actually contraindicated.

The Person with a Lesion

The "person with a lesion" can be either a patient or hospital personnel. Personnel in hospitals are definitely part of the epidemiologic cycle, as either victims[13,56,64,85,157,158] or sources,[4,13,63,159,160] or both, of staphylococcal infection not only to patients and other personnel in the hospital but also to their families. Lesions may develop, sometimes in large numbers, in both professional and nonprofessional personnel. For example, in a British hospital,[157] there were 146 cases of infection, mostly pyoderma, in one year among 725 nursing personnel, with an average loss of eight and a half days for each nurse. Patients can be admitted to the hospital with lesions or can acquire them during their hospital stay, not infrequently exhibiting them only after they leave the hospital. There is accumulating evidence that many patients are admitted to hospitals with "hospital strains" of staphylococci[13,65,66] acquired through indirect contact with the institution.

Cutaneous lesions, pulmonary infections and any lesion draining pus externally must be considered particularly dangerous from the point of view of dissemination of organisms into the environment and potential hazard to others. Adequate care must therefore include not only therapy directed toward the management of the individual patient but also measures toward preventing the spread of staphylococci to personnel, to other patients or into the environment. Isolation measures stressing aseptic technic are particularly important in this connection.

There is in addition a small group who appear to be at greatest risk of acquiring staphylococcal infection not from other people or from some source in the environment but from themselves. In certain patients with recurrent styes, superficial skin infections and minor industrial wounds in the community at large, as well as within hospitals,[161-164] it has been demonstrated that staphylococci carried in the nose can be related to the development of recurrent septic lesions. For this reason, topical nasal antibiotic therapy has been suggested to eliminate the assumed nasal reservoir of organisms. For instance, in one study,[164] 140 of 154 patients with positive lesion swabs were nasal carriers. Ninety-two per cent had organisms of identical phage types in both sites. The local (nasal) use of antibacterial cream decreased the number of recurrent lesions in the post-treatment as compared to the pretreatment period. In another study[162] 34 of 36 patients with recurrent styes were found to be carrying *Staphylococcus aureus* in their noses. Clearance of staphylococci after application of nasal ointment prevented recurrence of styes, which continued to occur in a control group. In both studies recolonization occurred in a majority of cases within four weeks, leading to the suggestion that patients should apply the ointment one week out of four.[164] A controlled study of the effect of topically administered antibiotics (nasal) has recently been reported from England by Tulloch et al.,[165] who studied 56 cases of recurrent furunculosis of at least six months' duration. Treatment consisted of an antiseptic cream (graneocidin or neomycin and bacitracin) applied to the anterior nares two or three times daily for at least three months. If eye swabs were positive, cream was similarly applied to the eyes. Hexachlorophene baths or powder was used for perineal carriers. Three of 23 control patients were cured spontaneously. Among the 33 test cases, however, 22 patients remained free of lesions for at least six months, 5 were cured when family sources of reinfection were eradicated, and 6 showed little or no improvement.

Agents other than antibiotics have been used either alone or as an adjunct to the treatment of staphylococcal infections. Bacteriophage therapy was occasionally used in the quarter century before the introduction of antibiotics. Although knowledge of staphylococcus phages is more specific than in preantibiotic days, the inherent problems remain.

The following considerations should be kept in mind in the use of phage therapy for the treatment of either individuals with lesions or carriers: getting the phage to the site of infection; the possible neutralizing effect of serum and pus; the possibility of reproducing in vivo what can readily be accomplished in vitro — for example, the conversion of one phage type of staphylococcus to another by lysogenization[55,56,71-73] (there is always the chance then of conversion to a strain of greater virulence); and the possibility of hypersensitization to the phage or products of lysis.

Therefore, it is suggested that, before it is applied to human patients, more evaluation be done with this form of therapy in laboratory animals.

Reports of the value of combined gamma-globulin and antibiotic therapy in laboratory animals[166,167] led to the clinical trial[168-170] of such combinations in a limited number of patients. Again, more work is

necessary to evaluate this adjunct to antibiotic therapy. It seems more likely, however, that specific immune therapy would be of greater value.

The Asymptomatic Carrier

The "carrier" may be defined from several frames of reference. One of the possible definitions depends on a bacteriologic assessment of whether the subject carries coagulase-positive staphylococci (usually in the anterior nares) and for what length of time he carries the same or other strains. Thus, those who carry the same or different types of staphylococci consistently for a long time are termed *persistent* or *chronic* carriers. Those who experience periods of consistent carriage of one strain alternating with periods of noncarriage of the same (or other) strains are termed *intermittent* or *transient* carriers. *Occasional* carriers carry staphylococci on rare occasions. The distribution of these groups in various studies among hospital personnel[171-173] is as follows: persistent carriers, 15 to 35 per cent; intermittent carriers, 15 to 50 per cent; and occasional carriers or noncarriers, 15 to 50 per cent. Over extended periods, detailed weekly culture observations of each individual in a small series of nurses[174] and medical students[175] help sharpen these definitions.

Another possible way of defining the carrier is based on the host-parasite relation. First of all, as mentioned in the initial section of this report, there appears to be a difference in the potential of various staphylococci to colonize various areas of the body.[80,176] For example, there are strains that colonize but do not appear to cause lesions either in the persons carrying them or in others exposed to them.[63,177] It would be most useful to be able to differentiate persons in whom the staphylococcus is causing no host reaction of any kind and others in whom the organism elicits some defense reaction in the body. Such a reaction could be termed a subclinical infection, as suggested by some investigators.[177] It might then follow that the organism carried, although kept in check most of the time by the carrier, may cause disease in another, susceptible person. Similarly, the organism may, because of some anatomic discontinuity or other phenomenon increasing the carrier's susceptibility, cause lesions in the carrier himself. Such a differentiation, based on host reaction factors, might be revealed by a systemic antibody response[101] or a local inflammatory response, presently under investigation.[178]

Except for the differing opinion of Vogelsang and Haaland[179] most students of the subject[177,180-183] have commented on the particular disposition of certain persons to the carrier state. Others either do not become carriers readily or are able to become free of their staphylococci after a short period. It has also been noted that close exposure of noncarriers to heavy carriers[177] or to patients with lesions[184] for long periods did not cause the carrier state to develop with any appreciable frequency. An exception to this may be the "cloud-baby" phenomenon,[185] in which infants become colonized as a result of exposure to a heavily disseminating infant carrier.

The fact that there may be different carrier sites suggests the possibility that many factors are active in determining the carrier state. It has been noted that staphylococci may be found in the nose, pharynx, umbilicus, axillae, perineum and stools, where they probably can multiply. They may also be found on the skin, face, hands and other parts of the body, probably a result of secondary spread. Recently, Roodyn[186] 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 superficial skin. In addition, he demonstrated persistent nasal carriage of the same staphylococcal phage type for over six years in 2 persons. Several observers have noted that the anterior nares[4,63,133] probably form the main reservoir site, although in occasional cases other sites, such as the throat, the perineum and the colon, may be more important.

Some have suggested that an anatomic abnormality in the nasal passages, such as polyps, spurs or a deviated septum, could be responsible for this difference. In one report[173] no correlation was found between the carrier state and abnormalities or infections of the nose or nasal sinuses. In another limited study[178] it was observed that abnormalities of the nasal anatomy occurred in several persistent carriers as well as several noncarriers. It may be that, although not the only factor, anatomic defects play some part in the complex that determines the carrier state.

Another possibility is that noncarriers have some inhibitory substance, perhaps a natural physiologic factor present in the nasal secretions. Such factors might not be present early in life, to explain the findings of nearly 100 per cent colonization in newborn infants on exposure[187] as compared to nearly 40 to 50 per cent in adults.[4,188] The fact that infants do not cry with tears until they are about six weeks of age, with resulting dehydration of the nasal mucous membranes, has been offered as a possible explanation.[189]

In adults, limited studies[173] have failed to demonstrate any difference in lysozyme content of the nasal secretions of carriers as compared to noncarriers. Indeed, lysozyme appears to have little effect in vitro on *Staph. aureus*.[41] The observations[190,191] that mucin (which probably affects phagocytic cells) from nasal secretions and saliva had a virulence-enhancing effect in animals offered a possible means of differentiation of carriers and noncarriers. Elek and Conen[84] found, however, that mucin had little effect on the virulence of staphylococci in human volunteers. It must be mentioned that these results were based on few trials and with mucin of animal origin.

Other possible inhibitory substances could be products of other bacterial commensals of the nose; elimination of these organisms with antibiotics would thus theoretically increase the incidence of staphylococcal carriers. This was found to occur in a study by Bernsten and McDermott.[192] These investigators hypothesized that the increased transmissibility of staphylococci in tetracycline-treated patients was a result of the drug-induced interference with the usual interspecies relations among the nasopharyngeal flora. Bacteriologic support for this concept was not found by these authors or by Duncan et al.[173] However, one report[193] noted that viridans streptococci isolated from the nasopharynx produced an extracellular antibiotic-like substance that suppressed the growth of *Staph. aureus* during the first eighteen to twenty-four hours of incubation. Other investigators[194,195] reported that the presence of staphylococci in the upper respiratory tract appeared to lessen the likelihood of finding other bacterial species and vice versa.

The question of replacement of nasal flora under antibiotic treatment has been studied intensively by Knight and his co-workers.[177,188,196,197] In early studies[196] it appeared that rates of acquisition of the carrier state were higher among patients receiving chemotherapy. However, later evidence led the authors to support the concept, not substantiated by Bernsten and McDermott,[192] that antimicrobial drugs do not affect the tendency of a noncarrier to become a carrier. They found that there was no increase in carrier rates of staphylococci in patients receiving tetracycline or penicillin. In addition, noncarriers treated with either of these drugs did not have more positive cultures during or after treatment than they had had before treatment.

There appear to be several possible explanations for the replacement of one strain in a carrier by a different strain, the simplest being that staphylococci residing on mucous membranes are replaced by others from the environment. This could be accepted more readily if the carrier's own strain were suppressed under systemic or local antibacterial therapy. Another mechanism has been suggested by Gould,[198] who observed that by serial passage in increasing concentrations of penicillin in vitro, he could convert penicillin-sensitive Group 1 and 2 staphylococci into penicillin-resistant Group 3 strains. These observations, unfortunately, lack confirmatory reports in the literature. However, without therapy, there is still the question of why a particular strain that is entrenched in the nose for several months is replaced by another one — and why that specific one out of all the others in the environment. It is conceivable that the replacing strain has some advantage over the original one, although Duncan et al.[173] could not demonstrate any difference in growth rates of the two strains. A replacing strain would have an advantage over other strains if it were lysogenic — that is, if it carried a bacteriophage that could lyse the original strain. Indeed, mixed cultures of lysogenic and susceptible strains in carriers have been noted in a few cases.[56,71,173]

Another question that arises is the origin of the colonizing staphylococci in the nose. Indirect evidence for origin via inspired air was offered by Thompson and Gillespie,[199] who decreased the carrier state in nurses who wore masks as compared to those who did not. More direct evidence was obtained by semiquantitative counts from the anterior nares, middle meatus, ethmoid areas and throat. It was found[178] that a much larger number of staphylococci were present in the anterior nares than in the other areas, by ratios of 100:1 to 10,000:1. Taking into account the technical difficulties of semiquantitative technics, as described by Knight et al.,[197] these findings suggest that staphylococci inspired with the air are somehow prevented from progressing further into the nose. This may be due to the action of cilia, physiologic substances and physical laws governing the movement of airborne particulates. The organisms then establish themselves in the anterior nares, where they can multiply. This site may be particularly permissive to multiplication because of the inspissated mucus so commonly found in the anterior vestibule of the nose. These results also offer further support for the anterior nares as a preferred site of culture rather than areas higher up in the nose.

It has been suggested[188] that the ability of carriers to disseminate their organisms may be related to the quantity of organisms carried. We have followed several persons in our laboratory, including noncarriers and occasional, intermittent and persistent carriers.[178] It has been found that the output of coagulase-positive and coagulase-negative staphylococci from the nares, measured semiquantitatively, varies between the nostrils, as well as with time. In persistent carriers, although the coagulase-positive staphylococci are recovered in different amounts each day, colonies picked were of the same antibiogram and phage type. On the other hand, colonies of coagulase-negative staphylococci, even from the same nares, showed different antibiograms. This suggests that there may be a relatively free exchange of coagulase-negative organisms, whereas coagulase-positive staphylococci seem more deeply entrenched.

Another possible means of differentiation among carriers is based on the work of Hare and Ridley,[200] who suggest that dissemination from carriers most probably does not occur directly via droplets or droplet nuclei such as are expelled during sneezing, coughing or speaking. They believe that there is spread first to anything touching the nose, such as hands, skin and clothing. Contamination of these areas by organisms carried in perineal areas has also been found to occur. From there, the organisms are dispersed into the air or come in direct contact with

other individuals. Walter[201] has suggested that the "dangerous" carrier is the one who disperses widely and can be recognized by repeatedly positive cultures from the hands, undergarments, skin, hair and so forth.

Still another possible route of transmission of staphylococci is suggested from reports of fecal carriers.[25,26,202] These studies showed that 20 to 40 per cent of adult patients are fecal carriers, the rate increasing during the hospital stay. The significance of this method of spread needs further evaluation.

The carrier state in newborn infants presents many interesting facets. Earlier workers[160] used nasal or throat swabs or both to culture staphylococci from newborn infants, assuming that babies became colonized mostly in those sites. However, later studies[187,203-207] pointed out the importance of other areas of the body such as the umbilicus and groin, which frequently become colonized in the newborn period before colonization of the nose or throat. These findings are of significance not only in the cultural procedures that should be used to detect newborn carriers but also in the methods of control necessary to manage the carrier state. Thus, the observation[204] that the umbilical cord is colonized within four days of birth in 80 to 88 per cent of newborn infants in large series suggests the need for culturing that site in carrier surveys as well as making it bacteria free. The incidence of actual sepsis of the umbilicus in these babies is very low, but they are still capable of spreading organisms in a nursery. The use of triple dye[203,207] (brilliant green, proflavin and crystal violet) or some antiseptic such as chlorhexidine (Hibitane) or hexachlorophene[206,208] has been recommended for the latter purpose.

Extensive culturing of various areas of the newborn infant's body was done by Gillespie et al.[205,206] and Hurst.[187] The latter demonstrated that the rate and sequence with which these body areas acquired *Staph. aureus* varied in two nurseries under study. Thus, in one nursery, 100 per cent of the babies were colonized by the fourth day at some site, and in another only 16 per cent carried *Staph. aureus*. Skin and rectal cultures usually became positive before those from the nose, throat and eye. In one nursery the groin and axilla became colonized before the umbilical cord, whereas in the other nursery colonization of the umbilical cord often preceded that of the groin or axilla. In addition, it was noted that different body sites became colonized with different strains of staphylococci and that two strains sometimes were detected in a single site. This study substantiated that of Gillespie et al.[205,206] The latter group also attempted to decrease the rate of colonization of various body areas, hoping to reduce the incidence of sepsis concomitantly. Hexachlorophene powder was applied to the trunk, buttocks, axillae, perineum and groin of babies, starting in the delivery room and continuing until the babies left the hospital. The incidence of colonization of all areas studied dropped markedly. However, the carrier rate in the nose was reduced only by about half. The incidence of skin sepsis fell from 6 per cent to 1 per cent. This supported the earlier findings of Baldwin and his co-workers,[80] who had used hexachlorophene baths to reduce colonization of the nose and groin of babies. Recent reports from Canada[207] and Australia[208] substantiate the findings of the British and American investigators of the value of hexachlorophene in the reduction of staphylococcal infection in the newborn period.

Before possible means of controlling the carrier state in adults are discussed a note on the recent emphasis on the self-infecting patient carrier should be included. The reports supporting this hypothesis as it relates to recurrent styes, superficial skin lesions and minor industrial wounds were mentioned in the previous section. Several reports, however, support the concept that patients who are nasal carriers are the source of their own wound infections. Weinstein[209] found that, in operations on 125 patients with an average stay of four months in the hospital, 37 per cent with positive nasal cultures contracted postoperative infections. In contrast, infections developed in 11 per cent of patients with negative nasal cultures. The finding of identical strains in the nose and wound of individual patients appears significant. Several questions relevant to mechanisms of acquisition of wound infection still remain. Were the nasal carriers perhaps not also skin carriers, as a high percentage are known to be? Was the infection acquired during or after the operation? Could these strains not have been found in personnel carriers as well, since the 80/81 strain isolated from 6 patients with infections is known to be prevalent among hospital personnel? Do these findings suggest some generalized staphylococcal "diathesis" among certain patient carriers, or some alteration of host defense mechanisms?

Williams and his co-workers[210] found that more carriers (7.2 per cent) than noncarriers (2.0 per cent) contracted wound infections. However, only about half the carriers had the same type of staphylococci in the wound as was carried in the nose. The same questions are raised in this study. Colbeck[211] cites a study of 384 patients who were later operated on. He found the rate of sepsis in nasal carriers to be sixteen times that of noncarriers, with the same phage type recovered from both nose and lesion.

Two possible mechanisms of such self-infections have been offered. The nose-to-wound route has been suggested by Walter,[212] who hypothesized that the nasopharynx is traumatized during anesthesia, allowing hematogenous dissemination of organisms to the susceptible wound area. Another explanation might be that the nasal carrier is also a "deep-skin" carrier, as demonstrated by Roodyn,[186] thus allowing infection to occur at the incision site.

Although the evidence is often indirect, the role of

the asymptomatic carrier as a source of outbreaks in nurseries and surgical units has been well established, as reviewed by Williams.[63] In other cases, however, the carrier is not considered to be too important. The oft-quoted report of Barber and Burston,[213] purported to demonstrate the greater importance of personnel with lesions, is based on 2 cases only. In one hospital[214] over 6 per cent of the nursing personnel on wards were carriers of the 80/81 strain; in another hospital the carrier rate was so high that a special carrier clinic had to be opened.[215] In view of the potential danger of some carriers and their great frequency in some hospitals, it becomes essential to develop reliable methods of management of the carrier. Several problems are inherent in any management program:

Methods of detection. The frequency of change in carrier status necessitates repeated surveys. It appears important to determine who the chronic (or persistent) carriers may be, as well as the site (or sites) from which dissemination occurs.

Definition of the potentially dangerous carrier. This is presently based on both epidemiologic and laboratory evidence.

It is well known that 20 to 70 per cent of hospital personnel may be carriers of coagulase-positive staphylococci. It becomes obvious, therefore, that a hospital could not be operated if all carriers were removed from patient care. Various studies have been directed at attempting to differentiate the dangerous carrier from the much more common innocent one. So far, however, the only available criterion is the type of staphylococcus that he possesses.[63] Thus, the hospital should first become aware of the strains that are epidemic within its walls. Carriers of these "epidemic" strains may or may not be related to infection in others. In some cases one can demonstrate this by epidemiologic studies relating that carrier in time and place to the start of an outbreak.[216] Frequently, however, either it is not feasible to demonstrate this possible relation, or the carrier may just as well be a victim as a source. In a few specific sensitive areas, particularly in nurseries for newborn infants, known carriers of epidemic strains might best be managed as described below. There are nevertheless many cases in which carriers of notorious epidemic strains fail to start epidemics and in which epidemics cease when carriers of the epidemic strain are still present.[63]

Because of these considerations management of the carrier is obviously not simple, and will depend in many cases on the circumstances within a particular hospital. Several approaches have been adopted with some success:

Informing the carrier of his status and potential danger to others, so that he was more aware of sound aseptic technic and personal hygiene, was apparently sufficient to stop surgical outbreaks in at least 3 reported cases.[217-219]

Having the carrier wear a special mask was helpful in 1 surgical outbreak.[220]

Use of various therapeutic agents has also been of some value.

Systemic antibiotics. This method has been used successfully to control skin and nasal colonization in infants who enter a contaminated nursery immediately after birth. The antibiotic should be given in full therapeutic dosage for one week.[160,176] It is recommended that antibiotic prophylaxis should be used only after very careful evaluation of the situation, and never for prolonged periods nor on a continuous basis.

In adults, Knight et al.[197] have demonstrated very clearly, using semiquantitative technics, that systemic antibiotics were only suppressive for a few days and that the same or resistant strains returned during or after therapy. Erythromycin was the most effective suppressive agent; tetracycline was less so, and penicillin was least effective. Methicillin also appears to be incapable of eliminating staphylococci from the nose, although it is effective for the treatment of lesions.[128,135]

Nasal administration of antibacterials. Gould[221-223] reviewed his large experience with the use of this method, and made the following observations:

Therapy is preferably reserved for persistent carriers.

The in vitro antibacterial sensitivity of the carrier strain must be determined.

Treatment consists of the application of various antibiotic creams, such as neomycin, bacitracin or combinations of drugs. The cream is applied 3 or 4 times a day to each nostril for a period of ten days.

Nasal therapy may need to be repeated at intervals of about one month. This is based on the observation that, although swabs taken during the course of therapy are negative in about 90 per cent of cases, the suppressive effect may persist for only a few days, so that after four weeks 40 to 80 per cent may have regained their positive carrier status.

In effectively treated carriers, there is at least 90 per cent reduction in the release of staphylococci into the environment.

The objections to and possible complications of the nasal use of antibiotic ointments include the possibility of selecting resistant staphylococci and increasing the number of carriers of resistant organisms, possible sensitization to the antibiotic used, alteration of the ecologic relations of natural nasal flora and contamination of the environment with the antibiotic.

Gould and Allan[221] claim to have reduced the incidence of crossinfection when carriers were treated. Rountree and her associates[224] reduced the incidence of neonatal staphylococcal infections by eliminating the carrier state of about 90 per cent of personnel carriers with the use of neomycin-bacitracin ointment. Klein and Rogers[225] described the nasal therapy of newborn infants as valuable in stopping nursery outbreaks of staphylococcal infection. In 1 hospital,[226] although neomycin ointment appeared effective in the majority of nasal carriers among the staff, some persistent carriers remained despite vigorous therapy. The authors considered the difference in results between staff and patients to be due to the density of infection in the wards and the greater chances of reinfection among those who were continually exposed in those wards.

One added comment should be made regarding the effect of neomycin on phage typing of staphylococci. Harrison et al.[227] found that, after graneocidin and neomycin-tyrothricin nasal therapy, 9 of 11 carriers of Type 80 strains grew *Staph. aureus* that could not be typed but showed the original type again after three weeks of repeated subculture. In vitro experiments revealed that subinhibitory concentrations of neomycin could change Type 80 strains into nontypable strains that, in subculture, reverted to Type 80.

Aerosol spray of penicillinase-resistant synthetic penicillin (methicillin): Elek and Fleming,[133] who believe that the crux of the problem of staphylococcal crossinfection lies in the nasal-carrier state, have evaluated a new technic for controlling this problem. They used an aerosol spray of methicillin, 4 gm. a day, in a maternity unit and demonstrated a progressive decrease in the rate of nasal colonization of newborn infants by coagulase-positive staphylococci. Rates of umbilical and fecal carriers were similarly decreased, as were actual staphylococcal infections.

Theoretical criticisms can be directed toward the use of this type of chemoprophylaxis. In addition to the dangers of sensitization and idiosyncratic reactions that attend the mass use of any drug, the possibility of selecting staphylococci resistant to methicillin (BRL 1241), a fear expressed recently by Barber,[135] will always exist. The problem of gram-negative organisms, resistant to the common antibiotics as well as to methicillin, that will also be selected in increasing numbers also remains. Nevertheless, it seems inevitable that this type of chemoprophylaxis will be attempted among surgical patients as well as other susceptible groups.

Use of hygienic measures. This is stressed by Rountree,[228] who believes that to eliminate the nasal-carrier state, the immediate and personal environment of the person must be made bacteriologically clean.

Use of bacteriophage therapy. The problems attending this type of therapy have been discussed. In newborn infants there is the added difficulty of the several sites of colonization. Even bacteriophage aerosols may not come into contact with staphylococci in the axillae or gastrointestinal tract.

Use of hexachlorophene washes. This method, discussed earlier, has recently been emphasized by Gluck et al.[229] They recorded a marked reducing effect of hexachlorophene washes on the colonization in newborn infants, not only of skin and umbilicus, but also of the nasopharynx.

Use of immunogenic agents. There is no definitive information on the use of vaccines or toxoids in the treatment of the carrier state.

Use of nonvirulent staphylococcal strains. The use of nonvirulent penicillin-sensitive strains to prevent colonization in newborn infants with more virulent strains has recently been reported.[230] Although this technic offers a new approach to the mechanics of the colonization and spread of staphylococci, it is doubtful whether it will prove to have practical application.

(To be concluded)

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