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THE EPIDEMIOLOGICAL VIRULENCE OF STAPHYLOCOCCI

INTRODUCTION

It has become apparent in recent years that exposure to the hospital environment can give rise to serious, sometimes fatal infection by hemolytic staphylococci. It is the purpose of this report to present data on the incidence of staphylococcal disease in human populations and to review evidence for unusual virulence in man of so-called hospital staphylococci.

Among many factors which have been thought to account for the apparent increase in nosocomial infection, four are predominant:

1. Advances in therapy have permitted prolonged survival of many patients with debilitating diseases. Hospital populations are coming more and more to consist of chronically ill, often elderly individuals who enter because of complications of disease or its treatment. The exposure of an increasing number of susceptible patients to the staphylococci that abound in the institutional environment has tended to favor development of serious infections.

2. Reliance upon antibiotics has undoubtedly led in many institutions to lowering of standards of cleanliness and neglect of techniques of asepsis and isolation, facilitating transmission of bacteria from hospital reservoirs to patients.

3. Staphylococci and other antibiotic-resistant organisms now abound in hospitals in great numbers. When a human population is exposed to an antibiotic, its bacterial flora is disturbed and eventually altered in favor of bacteria resistant to the drug. In Norway, where staphylococcal infections have been reportable for years, Lindan and Lofkvist[18] documented a striking increase in the frequency of staphylococcal infections of the newborn a few years after the introduction of the sulfonamides and penicillin. It has been shown that hospitalized patients are carriers of staphylococci more frequently than are nonhospitalized persons.[20] Knight *et al.* found that the carrier rate increases with the length of stay in the hospital and that patients who are treated with antibiotics are particularly likely to acquire staphylococci from the hospital environment.[12] Rountree and Barbour[15] were among the first to demonstrate that hospital personnel exposed to patients of this type develop higher carrier rates.

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4. It has been suggested that the staphylococci encountered in hospitals at the present time have greater virulence than those encountered in the pre-antibiotic era, or in nonhospitalized persons.

Virulence refers to the relative ability of an organism to produce disease. It is a controversial and ill-defined term, thought by some to be synonymous with pathogenicity. Virulence is dependent upon a number of factors (toxins, host, portal of entry, and so on), and is commonly measured by the number of organisms required to produce disease in a given system. Biochemical correlates of staphylococci such as pigment, hemolysin, and coagulase production are clearly not precise enough to estimate degrees of virulence for man. By means of bacteriophage typing, many staphylococci can be classed into strains, and an epidemiological estimate of virulence has become possible.

THE CONCEPT OF AN EPIDEMIC STRAIN

When hospital staphylococcal infections first began to receive attention, antibiotic-resistant strains belonging to the broad phage group III were generally incriminated.[11] In 1955, Rountree and Freeman[16] reported the isolation of a then nontypable and presumably uncommon strain from a nursery epidemic in Australia, and in 1956 the isolation of the same strain in Canada was reported by Bynoe *et al.*[5] This organism is a coagulase and mannitol positive hemolytic *Staphylococcus aureus* with the phage type 52/42B/47C/44A/80/81. It has recently been designated type 80/81. It is almost always highly resistant *in vitro* to the action of penicillin, streptomycin, and the tetracyclines, and usually susceptible to vancomycin, neomycin, bacitracin, kanamycin, erythromycin, novobiocin, and chloramphenicol. In the past two or three years this strain has become notorious because of the frequency with which it has been reported as the etiologic agent in hospital epidemics in the United States and many other parts of the world, and it is often loosely designated as "the epidemic strain." The question has naturally arisen as to whether this strain has been isolated so frequently from epidemics because it has an unusual propensity to incite disease or because it is merely commonplace in hospitals.

THE BEHAVIOR OF TYPE 80/81 IN HUMANS

There is a considerable body of information in the literature suggesting that type 80/81 has a greater tendency than many other strains of hemolytic staphylococcus to produce disease in infants and young children. In a nursery epidemic studied by Fekety *et al.*,[7] 34 of 49 (70 per cent) of the newborns who became carriers of the strain developed clinical infections

within the first few months of life. In contrast, only 3 of 92 (3 per cent) infants colonized by other coagulase-positive staphylococci developed clinical illness during the same period. In a similar outbreak reported by Wysham *et al.*[28] 78 per cent of the infants colonized by strain 80/81 developed clinical manifestations of infection, while only 31 per cent of those colonized by other staphylococci developed disease. They suggested that type 80/81 was of unusual virulence, but that it was not the only virulent strain in their nursery. Shaffer[19] and Wentworth[21] have reported similar attack rates for type 80/81 in newborns. In addition, the clinical observation has been made that type 80/81 has a tendency in infants to produce pneumonia, empyema, mastitis, and severe spreading cellulitic infections somewhat different from the characteristic abscess.[8, 10]

It has been suggested that the strain may be unusually virulent only for infants, and that the nursery may be the source from which the strain is disseminated to other parts of the hospital. There is evidence that the peculiar disease inciting powers of the strain are not limited to the nursery, however. Wentworth *et al.*[21] have studied the spread of this strain after its introduction into the family and community by the newborn. They have been impressed by the frequency of its transmission to family contacts, by the severity of subsequent infections, and by the stubborn persistence of the strain in the afflicted family. During their study, in 45 per cent of the families of infants who had been ill, one or more members developed suppurative disease, while only 9.5 per cent of the families without such contact had a similar experience.

Additional evidence that the strain behaves in an unusual manner even in otherwise healthy young adults was obtained during an investigation of an epidemic of type 80/81 infection in students at the veterinary school of a large university.[3] Many of the students had severe, recurrent skin infections, and the exact source of the outbreak was not determined. A survey showed that approximately 5 per cent of a group of controls recalled skin abscesses within the six months prior to being questioned. Gould and Cruikshank[9] reported similar rates for healthy persons. Ten per cent of the veterinary students who were subsequently found to be carriers of coagulase-positive staphylococci recalled such infections, but more than 50 per cent of those found to be carriers of type 80/81 recalled skin abscesses within the preceding six months.

Another example of the behavior of strain 80/81 in healthy adults was afforded by our studies on the persistence of carriage of staphylococci in the anterior nares of nurses and doctors from several hospitals. Cultures were taken at least once per week, and only those who carried the same strain for more than three weeks were included in the study. The results are shown in

Figure 1. There were 25 persistent or permanent carriers of type 80/81. The mean duration of carriage of the strain was 5.5 months, and many of the individuals were still carriers when the study ended. In contrast, the mean duration of carriage of other coagulase-positive staphylococci was only 3

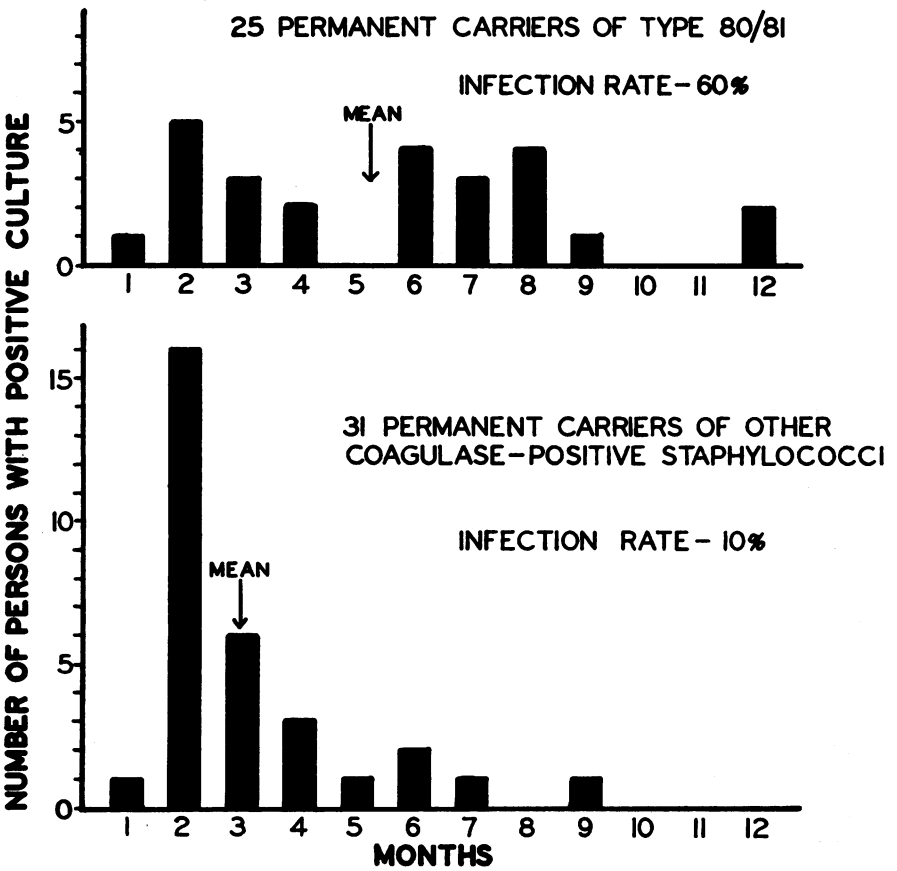

FIG. 1. The persistence of staphylococci in the anterior nares of adults.

months in 31 persons studied. During the period of observation 60 per cent of the persons carrying type 80/81 developed suppurative disease, while only 10 per cent of those carrying other strains were so afflicted. All of the type 80/81 carriers had been removed from the area in which they had presumably acquired the strain, though many of them probably were still exposed to the organism from time to time. Many of these presumably healthy individuals who were plagued by recurrent infections have been unable to rid them-

selves of the strain notwithstanding treatment with appropriate systemic antibiotics, the use of nasal antibiotic creams, and the adoption of various general hygienic measures. Many persons will respond to such treatment, but those who do not, give impressive testimony to the belief that it is not the lack of conventional immunity conditioned by prior experience with the organism which is responsible for the high rate of clinical illness observed.

In our studies concerning the kinds of staphylococci prevalent in a large general hospital under nonepidemic conditions, it was shown that although patients were being exposed to many different strains of staphylococci, type 80/81 was the one most commonly associated with disease. All of the staphylococci isolated from inpatients and outpatients at the clinical bacteriology laboratory of the Johns Hopkins Hospital from August 1, 1957 to April 30, 1958 were obtained by us and typed according to the bacteriophage method of Blair and Carr[1] using 25 phages. There were 900 isolates of *S. aureus* on which data sufficient for this analysis are available, and 75 per cent of these were typable. Although roughly 64 different strains were encountered, 31 per cent of the isolates were classed as type 80/81. There were 498 organisms from clinical infections, and 253 or 50.8 per cent of these were type 80/81. There were 402 isolates from the nose and throat, and the vast majority of these were asymptomatic infections not associated with suppurative disease elsewhere. Only 24 or 6.0 per cent of the isolations from the nose and throat were type 80/81. In 91 per cent of the instances in which type 80/81 was isolated, it was from a clinically recognized infection. In other words, type 80/81 isolates constituted a far greater proportion of the cultures from clinical infections than it did of the cultures from asymptomatic carriers. One conclusion which might be drawn is that type 80/81 organisms have a greater than average tendency to manifest their presence in a colonized host by a clinical infection. These results are summarized in Table 1. Since no other single type was encountered in appreciable numbers, the organisms there are divided into broad phage groups. Nontypable staphylococci, previously considered to be relatively nonpathogenic, were more outstanding in the nose and throat cultures than in those from infections. Although it was recognized that they are a heterogeneous group on the basis of antibiotic sensitivities, nontypable organisms were exceeded in frequency of isolation from clinical infections only by type 80/81.

Further examination of the data even more impressively implicated type 80/81 as the cause of hospital cross-infection during this study. Although only 31 per cent of the organisms isolated were type 80/81, 75 per cent of the clinical infections due to antibiotic-resistant organisms which had their onset after admission to the hospital were due to type 80/81. It should be emphasized that this study was performed under nonepidemic conditions.

TABLE 1. STAPHYLOCOCCI ENCOUNTERED AT THE JOHNS HOPKINS HOSPITAL AUGUST 1957 TO APRIL 1958

Type of staphylococcus (Blair and Carr[1])	*Total isolations*		*Isolations from infections*		*Isolations from the nose and throat*		*Per cent isolation of the strains from infections*
	Number	*Per cent of total*	*Number*	*Per cent of infections*	*Number*	*Per cent of nose and throat isolations*	
Group I	100	11.1	44	8.8	56	13.9	44
Group II	73	8.1	29	5.8	44	11.0	40
Group III	153	17.0	60	12.3	93	23.1	39
Nontypable	220	24.4	83	16.6	137	34.1	38
Miscellaneous	72	8.0	24	4.8	48	11.9	33
Type 80/81	275	30.6	253	50.8	24	6.0	91
Total	900	...	498	...	402	...	55

Only 1.5 per cent of the hospitalized patients developed staphylococcal infections. The cases were distributed evenly through the course of the study without concentration on a particular ward or service, and nursery infections were rarely encountered. A culture survey one month before the end of the study showed that approximately 5 per cent of the ward personnel and 4 per cent of the patients carried type 80/81. While staphylococci could be isolated with ease from the air, walls, floors, blankets, etc. in the hospital, type 80/81 was infrequently encountered in these sites. Under these endemic conditions one might have expected to isolate a variety of strains from the patients with infection. Since this was not the case, these data suggest that type 80/81 staphylococci were inordinately frequent agents of hospital infection, and that the strain therefore has greater virulence than many other coagulase-positive staphylococci.

DISCUSSION

Certain facts appear to be inconsistent with the thesis that type 80/81 has unusually virulent characteristics. McDonald[14] has studied a nursery where a high rate of colonization with the strain was followed by a low rate of subsequent illness. This staphylococcus was said to be identical in all measurable respects to the classical type 80/81; but since there may be variation within a type, these strains may not be identical. However, it is conceivable that the enhanced virulence we observed may be related to passage of the strain in human lesions.

It has not been possible to demonstrate that other staphylococci sharing the biochemical characteristics of type 80/81 are less virulent than it is for laboratory animals. However, Selbie and Simon[17] have presented data suggesting that the most important *in vitro* property related to the virulence of staphylococci for mice is alpha-hemolysin production; and Shaffer *et al.*[18] reported that only 6 per cent of 310 strains tested produced more alpha-hemolysin than did strain 80/81.

Elek[4] found that a million or more staphylococci were required to produce an infection in the skin of man following an intradermal inoculation, and that no differences could be found in the virulence of nasal or "lesion" strains, including one unidentified epidemic strain.[5] Since it is unlikely that most human infections are initiated by contact with a million or more staphylococci, it is probable that some host factor (such as an effect of skin oils or some condition at the base of hair follicles) permits the organism to multiply until it is able to overcome host defenses. Elek[4] found that the ability of his strains to initiate infection was enhanced five hundred fold by a suture at the site of inoculation, and he concluded that the circumstances of

the infection rather than the virulence of the organism determined the issue. However, if these circumstances or host factors favor a given strain more than others, it seems quite proper to refer to that strain as more virulent, for virulence always implies an interaction with the host. If one wishes to determine what it is about the host that is critical, it is then important to recognize that such factors may be particularly related to certain staphylococci.

Williams[22] has recently stated that the idea that all coagulase-positive staphylococci are of similar virulence can no longer be held. The data presented here suggest that type 80/81 is an unusually virulent staphylococcus, but it is by no means meant to imply that it is the only staphylococcus of increased virulence for man. Many recent epidemics have been traced to other strains, though type 80/81 has remained the outstanding epidemic strain.[23] Since it has not been possible to relate the virulence of type 80/81 to the number of organisms required to produce infection within the tissues, this property should be termed *epidemiological* virulence in order to avoid confusion with the term employed in animal studies.

Gillespie[8] briefly mentioned a hospital population colonized by an antibiotic-sensitive type 80/81 which appeared to be relatively avirulent, but there is no evidence that staphylococci made resistant to antibiotics *in vitro* thereby acquire enhanced virulence for animals or man. Similarly, there is no good evidence that the virulent antibiotic-resistant staphylococci encountered now are any more or less virulent than the virulent antibiotic-sensitive staphylococci encountered in the pre-antibiotic era,[2] and it does not seem likely that such data can be obtained. It does seem probable that virulent staphylococci have recently become more numerous, and that hospitals in particular have been seeded with these organisms, partly because of the frequency with which antibiotics are used there. Elek[6] has stated that "hospitals must be the Mecca of all truly virulent staphylococci, for the more severe the lesion, the more likely it is that the victim will make his pilgrimage to the hospital." The goal of further investigation is to prevent this strain from parasitizing new victims within the hospital.

SUMMARY

Type 80/81 staphylococci have gained recognition because of the frequency with which they have been associated with epidemics of suppurative disease in hospitals. The colonization of newborns by the strain is followed by an unsually high rate of clinical illness in the infants and their family contacts. Healthy adults appear to be unusually susceptible to the strain, for the strain persists for relatively long periods in the nares of adults and is associated with clinical illness in more than half of such cases. In one hos-

pital, the strain was isolated from 75 per cent of the cross-infections due to antibiotic-resistant staphylococci during a nonepidemic period when the strain represented a small segment of the staphylococcal flora of the hospital. It was concluded that the strain behaves epidemiologically as if it were more virulent than many other coagulase-positive staphylococci. Other staphylococcal strains with similar virulence probably exist, and there is no good evidence that these organisms acquire enhanced virulence for man when they become resistant to antibiotics.

The high frequency of hospital staphylococcal infections is related to the fact that virulent organisms have become more numerous in hospitals, in part because the spread and acquisition of such strains is facilitated by antibiotics. Many patients in hospitals are unusually susceptible to infection, and lapses in techniques of cleanliness and asepsis have increased their contact with bacteria. All of these factors must be taken into consideration if hospital staphylococcal infections are to be prevented.

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