Le 27 avril 1917, Cruchet, Moutier et Calmettes publiaient leurs observations sur "40 cas d'encéphalomyélite subaiguë," suivies quelques jours plus tard par un article venant du camp opposé signé de Von Economo sur une maladie semblable qu'il appelait *encéphalite léthargique*. On y décrivait de part et d'autre le tableau clinique d'une affection qui devait devenir avec l'influenza le point de départ d'une pandémie qui atteignit presque tous les points du globe. Le tableau clinique du début se modifia à mesure que la maladie se propageait. Les sequelles que l'on avait observées dans 50% des cas immédiatement après l'atteinte initiale se révélèrent de plus en plus nombreuses, et quelques unes apparurent seulement 20 ou 30 ans après la phase aiguë de l'attaque.

L'auteur fait part ici des faits cliniques que put observer le personnel du département de neurologie de la clinique Mayo chez plus de 1,000 cas d'encéphalite léthargique suivis pendant plusieurs années. L'épidémie apparut aux Etats-Unis dans l'hiver de 1918-19, sévit pendant plusieurs années et disparut graduellement vers 1927. La majorité était composée de sujets de moins de 40 ans bien que tous les âges en fussent atteints. Si les principaux symptômes étaient la somnolence et la diplopie, on n'en nota pas moins une foule d'autres tels que des impatiences musculaires, de l'insomnie, des tremblements, de la rigidité, des contorsions, de la persévération, des crises oculogyres, des troubles neurovégétatifs et endocriniens ainsi que des altérations du comportement et des perturbations psychiques. Le syndrome parkinsonien suivit l'infection dans 78% des cas.

Il est peu probable que le virus que soupçonnait Von Economo ne soit jamais identifié. Peut-être l'a-t-on déjà isolé depuis sans que rien ne puisse indiquer maintenant qu'il ait été jadis responsable de ravages si redoutables. L'encéphalite léthargique céda la vedette en 1933 à l'encéphalite de Saint-Louis qui fut elle-même suivie de plusieurs autres depuis.

NASAL CARRIAGE OF STAPHYLOCOCCUS PYOGENES BY STUDENT NURSES*

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MUCH INFORMATION has been accumulated in recent years about the carriage of *Staphylococcus pyogenes* in the human nose. Williams[1] in 1946 showed that skin carriage of staphylococci was secondary to nasal carriage, and that nasal carriers could be separated into those who harboured staphylococci constantly and those in whom carriage occurred only sporadically. Gould and McKillop[2] examined a large group of university students at weekly intervals for many months and were able to classify carriers further into three types: persistent, intermittent, and occasional. These workers also noted that some students never at any time carried staphylococci in the nose.

Many studies have been made of carriage of staphylococci by hospital nurses. These have shown that the carrier rate among them is higher than in the population outside hospital, and that nurses frequently harbour antibiotic resistant staphylococci, particularly strains causing cross-infection among patients. A number of investigators have made serial examinations of new entrants to nursing during their early hospital training to determine the increase in carriage during training, and the stage of training at which they acquire hospital strains of staphylococci. In three of these surveys[3-5] a marked increase was noted in the carrier rate within four or five weeks after the nurses finished their preliminary training and began ward duties. Hutchison and his colleagues[6], however, found no such increase in the number of carriers in the course of a long and careful survey of new nurses. All four groups of workers found that the nurses acquired antibiotic resistant staphylococci more frequently when they went on ward duty.

The object of the present investigation was to determine whether the increase in nasal carriage which has been described in nurses going on ward duty represents an increase in true long-term carriers, and to determine which hospital strains tend most readily to colonize the nose.

POPULATION STUDIED

In this hospital, new classes of student nurses begin training every six months. They spend four to five weeks in full-time classroom training and then work on the wards for only a few hours weekly until the 18th week, when they begin full-time ward duty. Three such classes took part in the study. Only three of the nurses in the first two classes and four in the third class had previous contact with a hospital, either

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as patients or nursing assistants. The details for each class studied are as follows:

Class 1—42 nurses. Weekly nasal swabs were taken for 18 months except when the nurse was affiliated to another hospital or was not available for other reasons. Fewer examinations were possible towards the end of the survey. The number of weekly swabs obtained from individual nurses varied from 30 to 48, with an average of 39, for the first 52 weeks; and from 37 to 63, with an average of 50, for the whole 78 weeks of the survey.

Class 2—9 nurses. Weekly nasal swabs were taken over a period of a year. The number of swabs obtained from individual nurses varied from 25 to 43 and the average was 31.

Class 3—53 nurses. Only a limited survey was undertaken. Nine swabs were taken from each nurse, two in successive weeks at the beginning of training, three in successive weeks in the fourth month of training, and four in successive weeks in the eighth month of training.

Laboratory Staff—For comparative purposes, a group of 15 bacteriology laboratory staff was examined. Twelve were followed up for 20 months, and three for nine months. Nasal swabs were taken weekly for the first 20 weeks and, because of the consistent findings in this group, at monthly intervals thereafter.

METHODS

Specimens were taken by rotating a moist cotton swab three or four times inside both nostrils. The swab was spread on a sheep blood agar plate, and was then placed in a tube of Maitland and Martyn's enrichment broth for staphylococci.[7] The broth was subcultured to blood agar if no staphylococci were isolated from the original plate. On the basis of cultural characteristics, one or more colonies were picked for coagulase testing. If coagulase positive (*Staphylococcus pyogenes*), they were tested for sensitivity to penicillin, tetracycline, chloramphenicol and erythromycin by a disc-plate method using the low and high strengths of Difco Disks for each antibiotic. All *Staph. pyogenes* isolated in the first year of the survey were typed with bacteriophage. Twenty phages were used, all of the international basic set,[8] except 71 and 80, and, in addition, phage 81 which lyses many staphylococci isolated in Canada.[9] Strains of phage and the strains of staphylococci on which to propagate them were generously supplied by Dr. E. T. Bynoe of the Laboratory of Hygiene, Ottawa. Typing was done first with phage at routine test dilution (R.T.D.), and strains which failed to type were later retested with phage at 100 x R.T.D. Occasionally, even if all colonies on a plate appeared similar, up to six colonies were picked for phage typing to determine whether more than one strain was present. Antibiotic sensitivity patterns were used in conjunction with phage types in determining whether strains were the same.

TYPES OF CARRIER

Fig. 1 illustrates the various patterns of carriage found in individual nurses and gives the number in classes 1 and 2 showing each pattern.

Constant carrier—Staph. pyogenes was cultured from the nose, usually in large numbers at almost every examination. In four nurses (8%), the same strain was isolated each time, and another four (8%) were constant carriers whose strains varied from time to time. In these, either the replacing strain overlapped the original one and eventually replaced it entirely, or a second strain was harboured for a time along with the original strain, and then disappeared. Rarely 3 different strains were present simultaneously. All these features of constant carriage are shown in the chart. Some nurses were classed as constant carriers even though they had negative swabs for varying short periods, but they seemed to fall into this classification rather than into the intermittent group. Constant carriers accounted for 16% of the nurses.

Intermittent carrier—Here, periods of consistent carriage alternated with similar periods of non-carriage. Consistent carriage is defined as the carriage of a strain of *Staph. pyogenes* for several weeks. This is considered true colonization. There were nine intermittent carriers (18%) whose colonizing strains remained the same; 13 (25%) carried different strains at each period of colonization. There were great differences in this group in the lengths of these periods of colonization, varying from 14 months' carriage followed by four months' non-carriage to colonization for only the last month of the survey. The differentiation of intermittent and constant carriers in borderline cases was somewhat arbitrary, but intermittent carriers could be distinguished from occasional carriers much more readily since only the intermittent carriers showed true colonization. A colonizing strain was recovered from 42% of all swabs taken from intermittent carriers. In addition, intermittent carriers occasionally, during phases of non-carriage, briefly harboured strains which failed to colonize the nose. In the whole group of nurses, 43% were intermittent carriers.

Occasional carrier—Small numbers of *Staph. pyogenes* were isolated on rare occasions in

this group, which consisted of 18 nurses (35%). In some a different strain was recovered on each of four or five occasions. In others, one strain was recovered on one occasion only. In a few, the same strain was isolated from two successive swabs, but these nurses seemed to fit better into the group of occasional rather than intermittent carriers. Each occasional carrier had an average of three positive swabs during the whole survey.

Non-carrier—This small group of three nurses (6%) consists of those from whom *Staph. pyogenes* was never isolated. It seems probable that these nurses do not differ significantly from occasional carriers. In both, a staphyococcus from the air must contaminate the nose periodically. Should this be recovered from a culture taken shortly afterwards, the individual would be classified as an occasional carrier. Non-carriers and occasional carriers together made up 41% of the group. In a few non-carriers, even the usual nasal flora of *Staph. albus* and diphtheroid bacilli was unusually scanty.

The laboratory staff showed the same patterns of carriage as the nurses, but fitted more readily into the different patterns. Of the 15 laboratory workers, six (40%) were constant carriers, four (27%) were intermittent carriers, two (13%) were occasional carriers, and three (20%) were non-carriers. Each constant and intermittent carrier had a single colonizing strain throughout.

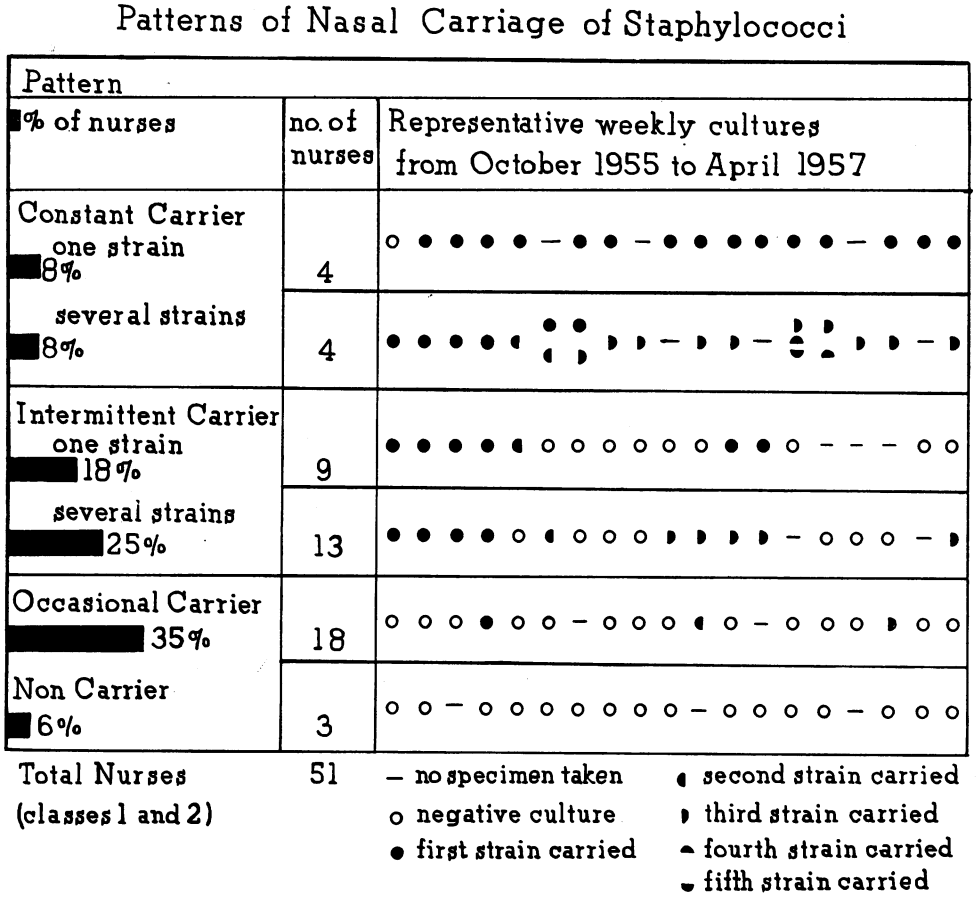

Fig. 1.—Patterns of nasal carriage of staphylococci.

INFLUENCE OF HOSPITAL ENVIRONMENT ON CARRIAGE

Carriage rate — It is evident from the different patterns of carriage encountered that the calculation of carriage rates from the number of positive swabs on any one day is inadequate. Such figures will include as carriers those occasional carriers who happened to harbour a few staphylococci at the time of swabbing. Another variation is introduced by occasional negative swabs from consistent carriers. These inaccuracies are apparent in the following carrier rates calculated for class 1 on a number of representative weeks: 1st week — 33%; 4th — 24%; 7th — 43%; 8th — 34%; 10th — 48%; 12th — 41%;

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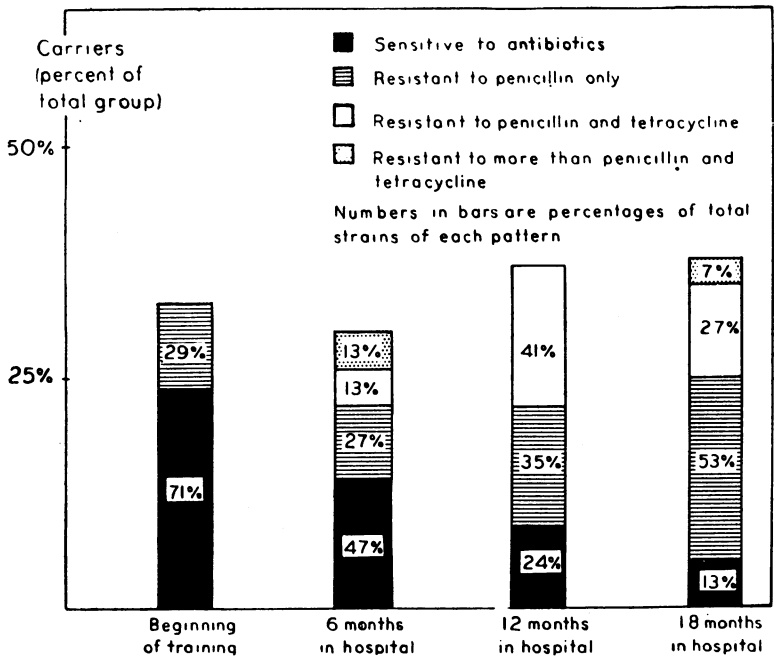

Fig. 2.—Incidence of carriers and antibiotic sensitivity of carried strains. Results from classes 1 and 2 (51 nurses).

15th – 38%; 21st – 37%; 25th – 24%; 32nd – 35%. It is clear from these figures that no valid comparisons can be made between carrier rates on different occasions if they are based on limited surveys.

A much better estimate of carriage rate would be one based on three or four consecutive weekly examinations from which might be calculated the proportion of individuals carrying staphylococci consistently. Fig. 2 shows carriage rates calculated in this way at the beginning, at 6 months, and at 12 months for classes 1 and 2, and at 18 months for class 1. Over the whole period, there was little change in the carriage rates, which remained between 30 and 38%. The rates for 53 nurses of class 3, calculated in the same way, were 36% at the start of training, 40% in the fourth month, and 28% in the eighth month.

Types of strains carried – While the carrier rates in nurses remained fairly constant throughout, there was a marked change in the type of strains carried, as shown by patterns of antibiotic sensitivity and phage types. The changes in antibiotic sensitivities are shown in Fig 2.

At the beginning of the nurses' training, 71% of the carried strains were sensitive to all antibiotics, but by 18 months only 13% were sensitive. Strains resistant only to penicillin increased from 29% at the beginning to 35% at 12 months. At 18 months, there had been a further increase to 53%, but the series was smaller. Penicillin-tetracycline resistant strains were not found at the beginning but by 12 months were 41%, and at 18 months were 27%. A few strains with other patterns of resistance were found at six months and 18 months.

With one exception, the penicillin-tetracycline resistant strains which appear in Fig. 2 were found to be of phage type 81. Most strains were lysed by this phage at R.T.D., but a few reacted only at 100 x R.T.D. The single strain failing to react was only tested at R.T.D. A few strains were also lysed by phages 52 or 52A. Strains sensitive to antibiotics were of various phage types, with a number failing to type. Strains resistant to penicillin only were mostly of group III, and those resistant to more antibiotics than penicillin and tetracycline were all of group III.

The nurses of class 3 also acquired, as their colonizing strains, more staphylococci resistant to penicillin and tetracycline than staphylococci

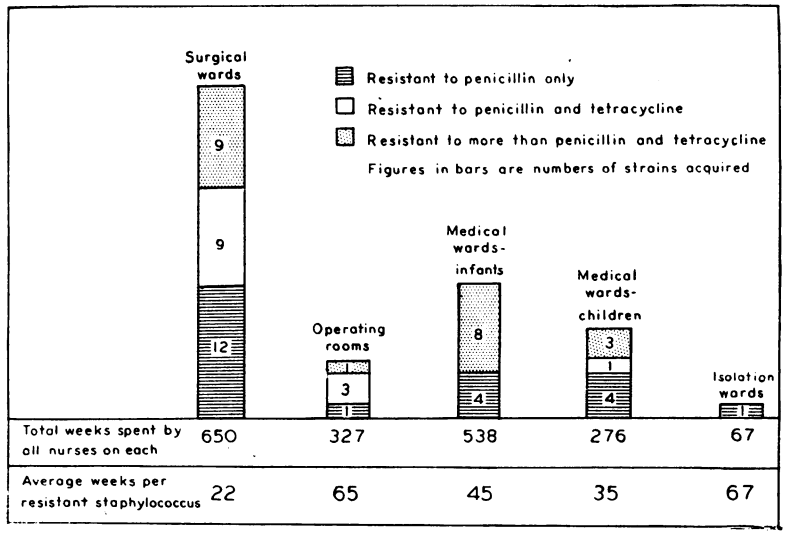

Fig. 3.—Wards where nurses acquired resistant staphylococci. Results from classes 1 and 2 (51 nurses).

of other patterns of resistance. At the eighth month of training, 26% of the carriers were consistently carrying penicillin-tetracycline resistant strains.

Differences within the hospital – Fig. 3 shows the relationship between the acquisition by nurses of antibiotic resistant staphylococci and the different parts of the hospital in which they worked. This analysis includes all resistant strains isolated, both colonizing and transiently harboured ones. On the surgical wards, the nurses of classes 1 and 2 picked up 30 resistant strains; 12 were resistant to penicillin only, nine to penicillin and tetracycline, and nine to more antibiotics. A total of 650 weeks was spent by the members of the two classes nursing on these wards. Thus, on an average, a resistant staphylococcus was acquired by a nurse every 22 weeks. Nurses in the operating rooms acquired resistant strains less frequently, on an average once every 65 weeks. In the infant medical wards, 12 strains were acquired, four resistant to penicillin alone, and eight to more antibiotics than penicillin and tetracycline. There, the nurses spent 538 weeks, and the average number of weeks to acquire a resistant staphylococcus was 45. In medical wards for older children, the average was 35 weeks. Only one strain was picked up during the 67 weeks spent by the nurses in the isolation wards. These figures show that there is a considerably greater chance of contamination of a nurse's nose by resistant staphylococci when she is working in the surgical wards than in the medical wards. It also appears, though the numbers involved are small, that the careful nursing procedures of the isolation wards lessen the chance of nasal contamination by resistant staphylococci in spite of the segregation in these wards of a large number of cases of staphylococcal sepsis.

The bacteriology laboratory environment had no influence in changing carried strains. All the constant and intermittent carriers kept the same colonizing strain throughout the survey, and these were either fully sensitive or resistant to penicillin only. The two occasional carriers had two positive cultures each during the whole survey, and these strains were fully sensitive or resistant only to penicillin.

NASAL COLONIZATION BY ANTIBIOTIC RESISTANT TYPE 81 STRAINS

Staph. pyogenes of phage type 81 and resistant to penicillin and tetracycline was carried for lengthy periods by a number of nurses, but other strains of staphylococci, although picked up frequently, less often remained as the colonizing strain. Long periods of colonization by penicillin–tetracycline resistant type 81 strains were observed on 10 occasions, but on only five was this strain found at a single isolated weekly examination. Thus, two out of every three times that the strain was found in a nurse's nose, it remained for many weeks as the colonizing strain. At the end of the survey, six were still present after being carried for periods of four, five, 13, 24, 44, and 48 weeks; four others were carried for 14, 17, 33, and 49 weeks.

Type 81 strains of other patterns of sensitivity were few; two were isolated only once, two were found as colonizing strains and one was carried by a nurse when she began training.

With group III strains resistant to more antibiotics than penicillin, there were six episodes of colonization and 18 occasions when the staphylococcus was found only once. Thus, these strains succeeded in colonizing the nose on only one of every four occasions they were encountered. Moreover, they remained as the colonizing staphylococcus for relatively short periods–two, three, six, seven and 13 weeks; one remained for 16 weeks and was still present at the end of the survey.

With antibiotic sensitive strains, there were 14 periods of colonization and 28 single isolations. With strains resistant to penicillin only, there were 16 periods of colonization and 21 occasions when the strain was isolated once. These strains include all phage types and some strains which were not typed.

In all, there were 36 periods of colonization during the survey by strains other than the penicillin-tetracycline resistant type 81, and 70 occasions when these miscellaneous strains were found on only one examination. This finding of one out of three contrasts with that found with the penicillin-tetracycline resistant phage type 81 and suggests that this strain has a greater tendency to colonize the nose than other staphylococci.

PHAGE TYPES

The phage types of 113 *Staph. pyogenes* of each pattern of antibiotic sensitivity isolated from nasal swabs from nurses during the first year of the survey are given in Table I. A strain isolated repeatedly from the same carrier

TABLE I.

Phage pattern	Sensitive to all		Penicillin resistant		Penicillin-tetracycline resistant		Other patterns	
	Nurse	Patient	Nurse	Patient	Nurse	Patient	Nurse	Patient
I. (R.T.D.)	9	—	2	—	—	—	—	—
I. (100 x R.T.D.)	1	—	—	—	—	—	—	—
II. (R.T.D.)	4	5	7	6	—	—	—	—
II. (100 x R.T.D.)	2	—	—	—	—	—	—	—
III. (R.T.D.)	4	1	12	2	3	7	21	11
III. (100 x R.T.D.)	5	—	4	—	—	—	—	—
81. (R.T.D.)	1	4	—	11	13	60	2	6
81. (100 x R.T.D.)	1	—	1	—	2	—	—	—
Mixed Group	1	—	1	4	—	1	—	—
N. T.* (only done R.T.D.)	2	18	1	11	1	7	—	1
N. T. (100 x R.T.D.)	12	—	1	—	—	—	—	—

*Not typable.

is considered a single strain in this analysis. Strains isolated only once are included. A separate series of 155 strains isolated from infected patients in the hospital was examined, and the phage types of strains of each sensitivity pattern are also shown in Table I.

The strains in both series were generally similar. Antibiotic sensitive strains and those resistant to penicillin only were distributed among the various phage groups. Most penicillin-tetracycline resistant strains from both sources were phage type 81, and this particular strain was the most frequent among staphylococci from patients. Strains resistant to more antibiotics than penicillin and tetracycline were almost all of group III; the remainder were type 81.

Type 81 strains isolated from patients and nurses were of practically all patterns of resistance from fully sensitive to resistant to penicillin, streptomycin, tetracycline and erythromycin, but few were fully sensitive. A number of group III strains showed lysis with phage 81 as well as with most of the group III phages. Type 81 seemed to share with group III staphylococci a marked tendency to be resistant to antibiotics.

IN VITRO INVESTIGATIONS

Strain replacement.—As described above, strain replacement was noted frequently in many carriers. Experiments were carried out in an attempt to explain this phenomenon. It was not found that the replacing strains could overgrow the replaced strains in broth. Such tests could be readily done when the strains differed in sensitivity, by carrying out viable plate counts on antibiotic-containing media. Attempts to detect the formation of antibiotic or other inhibitory substances by the replacing strain were unsuccessful. One replacing strain was shown to be carrying a phage capable of lysing the original strain. This finding could not be demonstrated with any of the other pairs of replacing and original strains.

Differences between carriers and non-carriers.—No correlation was found between carriage and abnormalities or infections of the nose or nasal sinuses. No consistent differences were found in the type of aerobic flora, other than *Staph. pyogenes,* of carriers and non-carriers. Tests so far have failed to show that the commensals in the noses of non-carriers produce substances capable of inhibiting *Staph. pyogenes.* Preliminary investigations have not revealed any marked differences in the lysozyme content of the nasal mucus of carriers and non-carriers. Strains of staphylococci from carriers have been tested for sensitivity to both nasal lysozyme and crystalline egg-white lysozyme and no bacteriostatic or bactericidal effect has been demonstrated.

DISCUSSION

The patterns of carriage described by Gould and McKillop[2] seem broadly applicable to hospital staff, although they were originally found in a predominantly non-hospital population. It is noteworthy, however, that the members of the bacteriology laboratory staff fitted the carriage patterns more closely than the nurses.

The nurses, being exposed to numerous staphylococci on the wards, showed a greater variation in carriage pattern within the four broad groups. Perhaps an equally satisfactory subdivision would be the grouping together of constant and intermittent as true carriers, and of occasional carriers and non-carriers as those peculiarly resistant to nasal colonization, and thus in effect non-carriers. Hutchison and his colleagues[6] also found that a proportion of nurses, despite the presence of many staphylococci in the ward environment, failed to become carriers. There seems little doubt that these individuals possess some host factor which prevents colonization by staphylococci. Our own experiments are not sufficiently far advanced as yet to prove or disprove the theory advanced by some workers that there may be differences in the lysozyme content of the nasal secretions of carriers and non-carriers. The very scanty total nasal flora in some of the non-carriers in our group might favour a non-specific mechanism but specific immunity may play a part. The absence to date of a satisfactory test for antibacterial antibodies against the staphylococcus as distinct from antitoxins seriously hampers the investigation of specific immunity, which might be effective locally.

The fairly constant carriage rate during the first 18 months of training in the nurses in this study is at variance with the findings of many workers. This is probably because most investigators have included occasional carriers by making use of the single swab survey. It is misleading to classify as a carrier a nurse of the occasional carrier group who has only a few contaminating staphylococci in her nose on isolated occasions. It has been shown that nurses picked up far fewer staphylococci in some wards of the hospital than in others, and that fewest were acquired in wards where nursing techniques and infectious isolation procedures were most efficient. Similar differences probably exist from one hospital to another, so that nurses in different hospitals would vary considerably in the frequency with which they would have a few contaminating staphylococci in the nose. This might account for the great differences in carriage rates, and the varying estimates of the increase in carriage among new nurses, which are given by workers who carried out single swab surveys. By including only those nurses who show true colonization of the nose as determined by three or four consecutive weekly examinations, this error is avoided. It seems likely that the high estimate of the increase in carriage in nurses entering the hospital environment has been accepted in much of the literature because the influence of occasional carriage has not been fully appreciated. Constant and intermittent carriers are probably the only ones of importance in disseminating staphylococci into the environment. Hare and Thomas[10] have shown that in intermittent carriers it is only when staphylococci are present in the nose that they are found on the skin and clothing, and that it is by way of these intermediate reservoirs and not from the nose directly that staphylococci reach the surroundings. The same is most probably true for occasional carriers and, since they have staphylococci in the nose for such short periods, they are probably not a source of appreciable staphylococcal contamination of their environment.

One of the most interesting findings in this survey has been the frequency with which nurses have acquired as their nasal colonizing strain, staphylococci of phage type 81 resistant to penicillin and tetracycline. The reason for this may be either that this strain has a particular capacity for colonizing the nasal mucosa, or simply that it is the one to which the nurses are most frequently exposed. The relatively rare occasions on which the strain was found only once without subsequent colonization, as compared with other resistant strains, tends to favour the hypothesis that it possesses a particular colonizing ability.

In this hospital, there has been a marked increase during the past five years in the incidence of staphylococci resistant to penicillin, streptomycin, and the tetracyclines, as has been reported elsewhere.[11] Phage typing of a series of these strains isolated in the last year showed that 85% were of type 81, and it is likely that most strains of this sensitivity pattern in earlier years were of this same type. Type 81 with this pattern of sensitivity has now become the most common strain in this hospital.

In 1956, Shaffer and his colleagues[12] reported an outbreak of staphylococcal infections in infants and nursing mothers in an obstetric hospital in Columbus, Ohio, due to strains of phage type 42B/47C/44A/52, and resistant to penicillin, streptomycin and chlortetracycline. These workers also found[13] that staphylococci causing

epidemics of nursery infection in hospitals in other parts of Ohio, in Michigan, in Wisconsin, in Philadelphia and in Seattle, were all of this same type. Bynoe in Ottawa tested Shaffer's strains and found that, with his phages, they reacted as typical type 81 strains. He believes that these discrepancies are due to the wider range of activity of the American phages, and that strains reported in the U.S. as type 42B/47C/44A/52 are the same as those identified in Canada as 81.[14] There have been other reports from Texas[15] of an outbreak of sepsis due to a staphylococcus of phage type 42B/44A/81 and resistant to penicillin, streptomycin, and the tetracyclines, and from Cincinnati[16] of similar infections by a strain of phage type 42B/44A/47C/52/81 and resistant to the same antibiotics. These strains are probably the same as phage type 81.

In Australia[17, 18] and Britain[8, 19] very similar outbreaks of infection in hospitals have been reported due to staphylococci of phage type 80. There is considerable evidence[9, 14] to suggest that these are the same staphylococci as those classified in Canada as phage type 81. Gillespie and Alder[19] found that this penicillin-streptomycin-tetracycline resistant type 80 strain appeared readily to colonize the nose. This is in agreement with our belief that the resistant type 81 strain possesses a particular capacity for colonizing the nose, and that this may in part account for the rapidly increasing prevalence of the strain in hospitals in different parts of the world.

Why a strain which has been carried for months should be replaced by another, such as a resistant type 81, and why some people are consistent carriers and others non-carriers, are questions which require much further work for their elucidation. At present, the only means of dealing with carriers of strains causing cross-infection in hospital are local treatment of the carrier's nose with antiseptic or antibiotic creams, which is at best only temporarily effective, and by the general measures of nursing hygiene to prevent the transfer of carriers' staphylococci to patients. The solution of the basic problems of strain replacement and of the underlying causes of carriage and non-carriage may well be also the solution of the practical problem of the management of carriers of hospital cross-infecting staphylococci.

SUMMARY

Nasal carriage of *Staph. pyogenes* was investigated in 104 student nurses during the first eight to 18 months of their training and in 15 laboratory workers. The strains found were identified by their antibiotic sensitivity patterns and bacteriophage types.

The patterns of carriage in 51 nurses intensively studied were: true carriers—59%, consisting of 16% constant and 43% intermittent carriers; non-carriers and trivial carriers—41%, consisting of 35% occasional carriers and 6% non-carriers. The laboratory group showed similar patterns.

Only constant and intermittent carriers showed true carriage defined as consistent carriage of the same strain for several weeks. On this basis, there was no real change in carrier rates during the course of the survey even after exposure to ward environments. The true carrier rates remained between 30% and 40%.

During the survey there was a marked change in the types of staphylococci found in carriers. Strains fully sensitive to antibiotics, which were of various phage types, fell from 71% initially to 13% at 18 months. They were replaced by other strains, particularly by penicillin-tetracycline resistant phage type 81. This particular strain seemed more capable of colonizing the nose than others.

Staphylococci of phage type 81, resistant to penicillin and tetracycline, were frequently isolated from infected patients in the hospital.

A greater number of resistant staphylococci were picked up by the nurses on the surgical wards than on the medical wards and least on the isolation wards.

Preliminary experiments have failed indicate why non-carriers resist colonization and why some strains of staphylococci replace others in the nose.

We wish to express our gratitude to the nurses who took part in the survey and to the staff of the nursing school for their unfailing co-operation throughout the investigation, and to Dr. L. E. Elkerton, Director, Division of Laboratories, Ontario Department of Health, who most kindly extended to us the hospitality of his laboratory during the propagation of phage stocks and the typing of staphylococci.

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RÉSUMÉ

Cent quatre étudiantes gardes-malades furent examinées pendant les premiers 8 à 18 mois de leur formation afin de découvrir la présence de staphylocoques pyogènes dans leurs fosses nasales. On examina de même 15 laborantines. Les souches furent divisées d'après le typage bactériophagique et la sensibilité aux antibiotiques. Cinquante-et-une élèves furent trouvées porteuses de germes. De ces porteuses chroniques, 16% hébergaient ces germes en permanence et 43% n'en gardaient que de temps en temps; 35% furent porteuses temporaires et rarement infectées. et aucun germe ne fut trouvé chez 6%. Des résultats semblables furent obtenus chez les techniciennes de laboratoire. Les porteuses constantes ou intermittentes seules ont répondu à la définition voulant que les mêmes souches de germes soient retrouvées chez les mêmes personnes pendant plusieurs semaines. A ce point de vue, on n'observa aucun changement dans la proportion de porteuses de germes pendant toute la période des recherches même après contact des malades dans les salles. La proportion des porteuses chroniques demeura entre 30% et 40%. Pendant le période de ces recherches on nota un changement considérable dans les souches de staphylocoques isolées chez ces porteuses. Les souches sensibles à tous les antibiotiques et de types bactériophagiques variés passèrent de 71% au début à 13% après 18 mois. Elles furent remplacées par d'autres souches résistantes à la tétracycline et particulièrement à la pénicilline, du type bactériophagique 81. Cette souche montra une facilité singulière à envahir les fosses nasales. A l'hôpital, ces mêmes souches furent souvent isolées de malades infectés. Les gardes-malades des salles chirurgicales portèrent un plus grand nombre de souches résistantes de staphylocoques que celles préposées aux salles médicales; les mieux protégées furent celles qui s'occupaient des cas d'isolement. On ne peut encore expliquer d'une part, la résistance des non porteuses à l'envahissement, et d'autre part, le remplacement de certaines souches de staphylocoques par d'autres souches dans les fosses nasales.

DIETHYLSTILBŒSTROL IN THE TREATMENT OF INOPERABLE CARCINOMA OF THE PROSTATE: A PRELIMINARY REPORT*

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THE INITIAL WORK of Huggins on the use of œstrogens in the treatment of carcinoma of the prostate has led to the development and use of various œstrogenic substances in this disease. Their exact mode of action has not been established. It is possible that their effects result from action through the pituitary gland by inhibition of gonadotrophins, from action through the adrenal gland, or from direct action on prostatic tissue. It is also possible that their effects result from other mechanisms as yet unknown. The pituitary mechanism is the one commonly accepted. The purpose of this study is to attempt to evaluate the use of one of these œstrogenic substances, diethylstilbœstrol diphosphate, in the treatment of carcinoma of the prostate. This substance has been supplied to us in the form of Honvol.†

Honvol is a stable solution of the disodium salt of stilbœstrol diphosphate (diethylstilbœstrol diphosphate). It has been postulated that the administration of a high dosage of œstrogen with a target release mechanism might be more effective than standard oral œstrogens. In the past, this has been impossible in the absence of a water-soluble drug. The problem has been overcome by the introduction of the disodium salt of stilbœstrol diphosphate, an inert material permitting high dosage and intravenous administration. Theoretically, the active monophosphate of stilbœstrol is liberated through the enzymatic action of acid phosphatase in tissues rich in this substance. Therefore, it is reasonable to presume that in the prostate, and other tissues which are the site of metastases from the prostate, a high acid phosphatase content may break down the diphosphate to the active monophosphate and allow for cytotoxic action. Experimentally, this cytotoxic action has been demonstrated by Druckrey, Danneberg and Schmaehl[1]. It has recently been shown[2] that, shortly after the intravenous injection of Honvol into rats, a fairly high concentration of stilbœstrol is found in the prostatic tissue and this concentration is maintained for some time. It does not appear to affect acid phosphatase activity in the prostate of the rat.

Frajola, Muhsin and Taylor[3] reported some results of a series of 13 cases treated with

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