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THE PROBLEM OF STAPHYLOCOCCAL INFECTION*

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The control of the great plagues and certain of the acute bacterial infections has not delivered mankind from infectious disease, but it has very decidedly changed the nature of that disease in certain countries of the world, including the United States of America.

The principal change in these countries has had the effect of throwing into prominence those bacterial diseases which characteristically require a relatively greater reduction of bodily defence before infection can become disease. To be sure, the initiation of any disease involving a particular microbe presumably requires some breakdown, however temporary, of the defence mechanisms of the host. Nevertheless, certain microbes seem to require more such help than others.

As we all know, the three principal diseases involving bacteria which are most prominent in the U.S.A. are those produced by the bowel flora, by tubercle bacilli, and by staphylococci. These three groups of diseases have a number of features in common; above all, they share together in the fact that harbouring of the parasite is commonplace but disease is rare. This means that the spread of these diseases among a group of persons is not to be regarded as a visitation from without but rather as an indication that something is going wrong with the crude equilibrium which had previously existed in that community.

If this is so, it follows that we should not be exclusively preoccupied with attempts to drive invaders out, for we are not really dealing with invaders but with original settlers. If they were not actually here first, they were certainly a close second. Indeed, in the specific case of staphylococci most babies acquire them during the first week of life. No, our preoccupation should be instead with attempts to discover what it is that goes wrong which permits these hangers-on to gain control; or, more specifically, with study of what there is to go wrong. And the fact that this indeed is a subject of widespread experimental preoccupation may be seen from the topics listed in our Conference.

Some Generalizations

Before concentrating exclusively on staphylococci, however, it might be helpful to recall to our minds certain of the other properties held in common by staphylococcal disease and its two sister diseases—those caused by tubercle bacilli and those caused by individual members of the bowel flora. There is, first of all, with

all three groups of diseases the fact mentioned previously that the presence of the microbe is commonplace, but disease and illness are rare. And this leads to that obvious inference that either the microbe or the host must undergo some significant alteration before infection can become disease. In addition, and with certain individual exceptions, there runs through the microbes of all three groups of disease the common tendencies: to produce localized lesions with destruction of tissue; to produce endotoxins or tuberculin; to survive intracellularly (only in the case of tubercle bacilli and staphylococci); to produce illness which may range from the exceedingly acute all the way to the barely perceptible chronic forms; and, finally, there is the common tendency to exist or to emerge in a form resistant to one or more antimicrobial drugs.

For these reasons, and even without respect to the matter of drug-resistance, the antimicrobial therapy of these forms of localized bacterial diseases has always represented a less important portion of the total therapy than is the case with certain of the acute relatively non-destructive microbial diseases.

Generalizations such as these are quite helpful when we are trying to outline and define a problem, but, as we all know, these generalizations soon reach their limits. And if there is one thing characteristic about staphylococci it is the complete lack of generality which they display with respect to many of the attributes related to disease-production in which we are most interested.

Thus, although we are gathered here to discuss something called staphylococcal infection we all know that this is not always quite the same thing as staphylococcal disease. We know, too, that even if we limit ourselves to the staphylococci which regularly produce the aureus pigment and coagulase, or even to the members of the same bacteriophage type, we are not necessarily on firm ground with respect to their homogeneity in terms of ability to initiate disease in man or some laboratory animal. At times it almost seems as if every staphylococcus is different.

The Microbe and the Lesion

In addition to the strong individualistic tradition among staphylococci, consideration of the subject of staphylococcal infections or disease is further complicated by the very real difficulties in establishing a diagnosis. We have here the same general problem that we face with any ubiquitous microbe, but with the added obstacle that we know that staphylococci are capable of producing lesions virtually anywhere on the body surface and that human carriers of staphylococci are commonplace. As a consequence, we cannot accept the mere

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presence of staphylococci in an open lesion such as a wound—even an operative wound—with any degree of confidence that the microbe and the lesion are necessarily related. In short, open wounds in open wards, no matter how carefully the wound may be protected by surgical dressing, are seldom suitable objects for the study of staphylococcal infection and disease, yet we know that some of these lesions could be related to the staphylococci.

Accordingly, in considering staphylococcal infection and disease, one must limit the discussion to lesions which had never shown external drainage at the time of first culture—that is, the so-called “closed lesions” and the infections accompanied by bacteraemia. Even with the so-called “closed lesions” the chance of contaminating the lesion by an irrelevant staphylococcus is present, but can be minimized with proper care.

These points are quite well known to all of us. Nevertheless, I am convinced that we who are familiar with them have almost completely failed to communicate them to our scientific colleagues not directly connected with the staphylococcal field. We have sinned further, in my opinion, by not clearly pointing out that most of the large-scale clinical investigations on drug-resistant staphylococci were not concerned with staphylococcal disease at all but had to do with something quite different—namely, the healthy carriers of staphylococci. Finally, while I am on the subject of our sins, until recently we quite failed to emphasize something we all knew—namely, that a penicillin-susceptible staphylococcal infection in a patient virtually never becomes drug-resistant during therapy. As a result of this failure in ordinary communication I am quite confident that physicians and others interested but not directly engaged in the field have the misconception that the number of patients with actual drug-resistant staphylococcal infections and disease seen each year on a general hospital service can be numbered in the hundreds. They have the further misconception that if one treats a penicillin-susceptible instance of serious staphylococcal disease with penicillin the drug will soon prove valueless because of the emergence to predominance of drug-resistant staphylococci.

Exposure in Hospitals

With full appreciation of the problems presented by this individualistic tradition of staphylococci and the difficulties in diagnosis, let us turn now to the question of the staphylococcal problem as we face it to-day. Let us also try to see whether the problem is significantly different from that presented a decade or so ago.

First, let us ask whether our population at large or the special population in our hospitals are experiencing any greater exposure to staphylococci than was the case ten or twelve years ago. Fortunately, we have careful studies bearing on this point available, and it appears that the answer is “No.”

We have, for example, the detailed studies of A. A. Miles and his associates in England which were published in 1944, and we have many studies with the phage-typing method conducted in widely separated portions of the world during recent years. All of these studies show substantially the same thing.

Approximately one-half of any group of adults not in hospital are nasal carriers of staphylococci when studied at a single point in time. When members of the group are followed individually for periods of several weeks or longer, the percentage harbouring staphylococci at one time or another goes up and may reach 70 or 80%. Likewise, when patients are studied on first admission to a hospital and then throughout a hospital stay, the percentage harbouring

staphylococci goes up appreciably from the 50% level on admission and then tends to fall back again after discharge.

One of the many interesting observations brought out in this type of study has been the indication noted by Miles *et al.* (1944), who stated: “The nasal carrier state varies, not with the environment of the person, but with the person himself. There is a marked tendency for persons to be either persistent carriers* or persistently free from nasal *Staph. aureus*.”

Thus, in answer to this first question it can be said that there is no indication that our degree of exposure to staphylococci either in or out of our hospitals is any greater to-day than it was twelve years ago. This is not particularly surprising, and is perhaps just another way of saying that staphylococci were plentiful then and are plentiful now.

The Problem of Pathogenicity

The next question which arises is whether there is any reason to believe that strains of staphylococci of enhanced pathogenicity for man are more prevalent to-day than ten or fifteen years ago. This question is less readily answered than the previous question, because of the nature of the problem. However, if such an increased prevalence of more pathogenic staphylococci was occurring it would be most readily apparent in the number and the clinical forms of the staphylococcal disease seen in patients on admission to the hospital.

Infections which occurred in the hospital environment itself would not provide much information on this subject unless the infections were truly overwhelming. The reason for this is that in a hospital population the presence of so many people ill with other diseases, or ill as a consequence of treatment, would make it difficult to distinguish in any individual situation between increased pathogenicity of the staphylococci and decreased resistance of the host.

So far as concerns patients newly admitted to hospitals, there appears to have been surprisingly little attention directed to this point in recent years. Everyone seems to agree that one of the commonest forms of serious staphylococcal disease, the primary haematogenous osteomyelitis of childhood and adolescence, has virtually disappeared from our admitting-rooms. I also suspect, but cannot substantiate, that patients with carbuncles and recurrent boils are seen less frequently requesting admission to the hospital than was the case ten or fifteen years ago. In several of the recent reports—for example, one by Barber and Burston (1955) from London a few months ago—the number and the form of staphylococcal disease seen in patients on admission to the hospital are listed, but no comment is made concerning how the material compares with the experience in years past.

Fisher *et al.* (1955) reported that in the twenty-year period, 1933–53, at the Johns Hopkins Medical Center, slightly over one hundred patients with staphylococcaemia were seen. This number presumably also includes patients who developed bacteraemia while in the hospital. Nevertheless, the crude figure of 5 to 10 patients admitted annually with staphylococcal bacteraemia would be about what has been seen at New York Hospital–Cornell Medical Center. It should be mentioned, however, that admission rates of patients with staphylococcal bacteraemia to the large university centres may give a falsely high value because of the tendency to transfer such patients from a smaller hospital after therapeutic failure.

Another serious form of staphylococcal disease, the primary pneumonia of adults, tends to occur in sporadic outbreaks in association with viral influenza. Hence it is difficult to form an estimate of its general annual incidence. By the same token, it seems safe to say that there has been no recent steady increase in primary staphylococcal pneumonia in non-hospitalized patients. Such an increase, related or unrelated to influenza outbreaks, might be expected if strains of appreciably enhanced pathogenicity for man were becoming more prevalent.

* Italics mine.

There is one entity, the staphylococcal empyema of infants, particularly those under the age of 6 months, which has been reported to be on the increase. This entity probably represents a situation which is closer to that of the development of infection *in the hospitalized patient* than to *the adult coming to the hospital* with established staphylococcal disease. Hence if there is an increase in this entity—and the fact that a real increase has occurred is by no means clear—it should be considered in relation to the problem of the development of staphylococcal disease by persons with hospital experience.

With this possible exception, however, there is remarkably little to suggest that there is any notable increase in the number of patients, particularly adult patients, appearing at our hospital admission rooms with staphylococcal disease. Moreover, there is nothing to suggest that the forms of the staphylococcal disease seen represent the dissemination of more malignant strains of the microbe or the concentration of more malignant strains in particular localities outside our hospital. Indeed, the one apparently definite change in the form of staphylococcal disease seen is for the better—namely, the virtual disappearance of the serious diseases of primary haematogenous osteomyelitis.

The type of evidence available on this question of the form and numbers of patients with staphylococcal disease requesting hospital admission is admittedly sketchy. Nevertheless, while much has been published on staphylococci in recent years, no one seems to be mentioning any remarkable increase in the number of patients with staphylococcal disease or any increase in unusually malignant forms among the patients who present themselves for admission to hospital.

Is there an Increased Virulence?

We have therefore a situation in which neither our patients in hospitals nor what might be loosely termed the public at large are apparently undergoing any greater exposure to staphylococci than was the case a decade or so ago. And we have no particular reason to believe that there has been a wide increase in the prevalence of unusually pathogenic staphylococci or even that there has been any substantial numerical increase in staphylococcal disease occurring outside our hospitals.

In brief, we have no convincing evidence, or indeed even any particularly well-founded suspicion, that *the crude equilibrium between the public at large and the ubiquitous staphylococci is shifting for the worse*. If any shifts have occurred they seem to have been on the side of a more favourable situation for the members of the public.

What, then, is the situation of our special communities of hospitalized patients with respect to their crude equilibrium with their staphylococci?

As mentioned before, their risk of exposure to staphylococci *in general* is presumably no different from what it ever was—or at least from what it has been in the past decade. But how about the possibility that there is a wider prevalence of particular strains of increased pathogenicity for man? Because of the localized and highly special circumstances involved, is it not possible that especially pathogenic strains of staphylococci might be lurking around our hospital environments, whereas the same strains would not be so readily detectable when spread through the community at large?

Let us set a measure of increased virulence in terms of epidemics of unusually serious staphylococcal disease involving a dozen or more patients at a time in a single hospital and occurring throughout our hospitals in general. Viewed in these terms I do not believe that we have a particularly good case for increased virulence of the so-called "hospital staphylococci." But when one considers the highly individualistic nature of staphylococci it is by no means inconceivable that such strains are present here and there, though operating, thus far, only in terms of tiny localized epidemics. Indeed, there is some reason to believe, in the case of a few strains, notably the enterotoxin-

producing strains, that this sort of thing is actually happening even though its overall numerical expression is still quite small.

Even this occurrence of tiny but multiple epidemics involving enterotoxin-producing staphylococci, however, does not establish that these strains are necessarily newcomers to our hospitals or necessarily have assumed increased virulence for man. For we are obviously doing other things to our patients which we were not doing in years gone by, and it may be that *it is the setting rather than any absolute increase in microbial virulence* which determines this highly alarming phenomenon.

There is another phenomenon, re-emphasized by Barber and Burston (1955), which might indicate that the staphylococci prevalent in our hospitals to-day have an increased pathogenicity for man. In brief, they have presented evidence that strains of staphylococci from the lesions of active staphylococcal disease may be the chief offenders in terms of cross-infection and the ability to initiate staphylococcal disease in new hosts. It should be emphasized that these investigators do not present their findings as evidence that the lesion-producing staphylococci are necessarily more virulent than the more virulent of our present strains. They merely suggest that it is these lesion-producing staphylococci which have the capacity to initiate new disease, in relative contrast to the staphylococci of the nasal carriers.

These observations made by Barber and Burston with modern techniques are particularly timely and should form the basis for detailed epidemiological investigations. Hence it is no disparagement to point out that their findings recall to mind the well-respected item in the clinical lore of our fathers' generation to the effect that a hand infection in a surgeon or a pathologist was a far more dangerous thing than a hand infection in a housewife who had stuck herself with a pin. It was reasoned that the strain of microbe in the case of the surgeon or pathologist was more dangerous on the grounds that it had been so recently producing disease in a patient.

Although these last few remarks on hospital staphylococci are relevant to the central topic they represent a slight digression from the consideration of whether to-day's hospital staphylococci contain an impressively increased prevalence of unprecedentedly virulent strains. On this subject, I believe it can be said that when one considers the wide range among individual strains of staphylococci in terms of ability to initiate new human disease, there is no convincing evidence that—on the whole—our hospital staphylococci are any more virulent for man than they ever were.

Lowering of Defences

As I see it, therefore, we are not subjecting our patients in hospitals to a greater risk of exposure to staphylococci or to any more especially virulent strains of staphylococci than we ever were.

Does this mean that we are not seeing the development of more staphylococcal disease among our patients while they reside in our hospitals to-day than was the case a decade or so ago? Almost certainly not. Indeed, the only reason for qualifying the situation at all is the lack of precise comparative data for the two time periods. Despite the absence of precise data, I am confident that most of us are convinced that to-day we are seeing with greater frequency the actual development of staphylococcal disease in patients *after* they have come into our hospitals than was formerly the case. In short, we are beginning to detect signs that the hitherto satisfactory equilibrium between our hospital patients and staphylococci is becoming unbalanced.

It is not so much that our patients in hospitals are being subjected to any greater challenge by staphylococci as it is that they are less well equipped to meet the same old challenge. Because they are less well equipped, it is up to us to give them better protection. At the present time, however, we are doing considerably less than that. Indeed, in many cases we are actually lowering such defences as the patient brought with him to the hospital. We are doing

this by the bodily disturbances we create as an unsought-for accompaniment of many of our modern therapies. In effect, an unfortunate by-product of our life-saving and life-prolonging procedure is to create a favourable market for staphylococci.

This favourable market is being created in several ways. First, our modern therapies are permitting the survival of people who are less able, in various undefined ways, to cope with bacterial infections. Examples of this sort are the insulin-treated diabetics, the children who have had splenectomies for various haematological disorders, the adults who have had total gastrectomies, and perhaps even some who have had partial pulmonary resections. Second, certain of our commonly used treatments such as cortisone, hydrocortisone and corticotrophin, the more widely acting antimicrobials, and x-ray irradiation are known to create circumstances which at times facilitate the development of infection. It is conceivable that on certain occasions treatments such as the antihistamines or the anticoagulants might unfavourably influence infection. Finally, in order to manage many of these modern treatments properly, it is necessary to perform venepunctures and skin punctures with unusual frequency on these very patients who for one reason or another are more liable to the development of infection.

To be sure, this increased congregation of more susceptible hosts in our hospitals is not necessarily the only reason for the apparent increase in staphylococcal infections developing in the hospital. Nevertheless, it does seem to be the principal factor which is *different* in our situation to-day from that of a decade or so ago. Moreover, if it is happening in the hospitals to-day, it is reasonable to expect that it will happen outside the hospitals in the future as these various forces become active on a wider scale.

If we assume the validity of this analysis, how can the situation be improved? It would be pointless to think in terms of attempting to oppose many of the forces which are contributing to this situation, because so many of these forces are such notable scientific achievements for the common good. Moreover, as staphylococci are so ubiquitous, an approach based on attempts to eliminate them from the environment would not seem hopeful. In the same way, it does not appear that antimicrobial drugs *per se* would play an important part. Chemoprophylaxis is a two-edged sword at best. In the present situation, the necessity for protecting the patient for such very long periods against a number of microbial species in addition to staphylococci makes the use of drugs impracticable.

Two approaches exist which seem reasonable. The first is for us all to have a continuing awareness of the fact that our hospitalized patients to-day are on the whole less able to cope with staphylococci than was formerly the case. This means that we should review and probably intensify our aseptic practices not only in the operating-room but especially in connexion with the ordinary "puncture" procedures used in the wards.

The second approach is the major one—namely, to find means for increasing bodily defences against staphylococci and means to restore these defences when they have been reduced. The logic of this approach is evident if you agree with me that the crux of to-day's staphylococcal problem lies not so much in changes in our staphylococci as it does in changes in the status of our hosts. Our difficulties with this second type of approach arise immediately, however, and stem from the fact that we are almost wholly ignorant of the mechanics of staphylococcal infection and disease. Until we can discover more than we now know concerning what determines the pathogenicity of certain staphylococci and how the healthy host manages to live in peace with them, it is not likely that our situation will materially improve.

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THE TRANSMISSION OF STAPHYLOCOCCUS AUREUS

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There is now a great deal of evidence that a high proportion of the staff of many hospitals are nasal carriers of penicillin-resistant *Staph. aureus*, that they soon acquire them after coming into residence (Barber, Hayhoe, and Whitehead, 1949; Rountree and Barbour, 1951; Barber and Burston, 1955), and that similar strains are responsible for sporadic infections of clean operation wounds and for outbreaks of conjunctivitis, mastitis, and pemphigus neonatorum in hospital nurseries. Although this suggests that the nasal carrier is primarily responsible for such infections, it is possible that transfer of organisms from minor staphylococcal infections such as boils, styes, or acne pimples on the person of members of the staff who have remained on duty may be equally important.

Attempts to prevent transfer of infection from either of these two sources are, however, hampered by our lack of knowledge of the methods by which *Staph. aureus* is transmitted from person to person. Except for the work of Duguid and Wallace (1948), little attention has been paid to this. The experiments reported in this paper were designed to throw further light on this question.

Experimental Methods

The manner in which experiments were carried out is given in the appropriate place in the text. It is, however, necessary to give some general details of the methods employed.

Media and Identification of Colonies.—The medium consisted of 1% Lemco agar, and in some of the early experiments an attempt was made to pick out colonies of *Staph. aureus* by their colour, consistency, and behaviour in coagulase tests on slides. In most of the experiments, however, phenolphthalein diphosphate (0.01%) was incorporated in the medium at the time the plates were poured. The majority of strains of *Staph. aureus* (Barber and Kuper, 1951) produce arylphosphatase, with liberation of free phenolphthalein in and around the colonies, which can be detected by a red colour developing when the culture plate is held over the open neck of a bottle of strong ammonia. All plates were examined in this way after incubation for eighteen to twenty-four hours, and counts made of colonies which had a red coloration and which resembled those of *Staph. aureus*. When necessary, subcultures were made in broth, coagulase tests being carried out by the tube method (Fisk, 1940).

Total colony counts were made after incubation for a further 24 hours.

Expression of Results.—The time of exposure of the plates varied in different experiments, and in order to secure uniformity the results are expressed as the number of organisms (or *Staph. aureus*) falling on to 1 square foot (930 square cm.) of medium in one minute.